Pest Management Regulatory Agency
Agence de réglementation de la lutte antiparasitaire

Regulatory Note

REG2000-14

Kresoxim-methyl Technical
Sovran® Fungicide

The active ingredient kresoxim-methyl and the formulated product Sovran® Fungicide, containing kresoxim-methyl for the control of apple scab and powdery mildew in apple orchards in Canada, have been granted temporary registration under Section 17 of the Pest Control Products Regulations.

This regulatory note provides a summary of the data reviewed and the rationale for the regulatory decision concerning these products.

(publié aussi en français)

October 20, 2000

This document is published by the Submission Management and Information Division, Pest Management Regulatory Agency. For further information, please contact:

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Foreword

Health Canada's Pest Management Regulatory Agency (PMRA) has issued a temporary registration for Sovran® Fungicide, a fungicide developed by BASF Corp. for use in apple orchards. Sovran® Fungicide, which contains the active ingredient krezoxim-methyl effective against apple scab and powdery mildew. The product will be sold and used for the first time in Canada during the 2000 growing season.

Methods for analyzing kresoxim-methyl residues in environmental media are available to research and monitoring agencies upon request to the PMRA.

BASF will be carrying out additional environmental and occupational exposure studies as a condition of this temporary registration. Following the review of this new data, PMRA will publish a Proposed Registration Decision Document and request comments from interested parties before proceeding with a final regulatory decision.

Table of Contents

1.0 The active substance, its properties, uses, proposed classification and labelling 1
- 1.1 Identity of the active substance and preparation containing it 1
- 1.2 Physical and chemical properties of active substance 2
- 1.3 Classification and labelling 3
  - 1.3.1 Technical kresoxim-methyl 3
  - 1.3.2 Sovran® Fungicide (48.4% kresoxim-methyl) end-use product 3

2.0 Methods of analysis 3
- 2.1 Method for analysis of the active substance as manufactured 3
- 2.2 Method for formulation analysis 4
  - 2.2.1 Multiresidue methods for residue analysis 4
  - 2.2.2 Methods for residue analysis of plants and plant products 4
  - 2.2.3 Methods for residue analysis of food of animal origin 5
  - 2.2.4 Analytical methodology for environmental substrates 6

3.0 Impact on human and animal health 6
- 3.1 Integrated toxicological summary 6
- 3.2 Determination of acceptable daily intake 8
  - 3.2.1 Non-carcinogenic end points 8
  - 3.2.2 Carcinogenic end points 9
- 3.3 Acute reference dose 9
- 3.4 Toxicology end-point selection for occupational and bystander risk assessment 9
- 3.5 Impact on human health arising from exposure to the active substance or to impurities contained in it 10
  - 3.5.1 Operator exposure assessment 10
  - 3.5.2 Workers 11

4.0 Integrated food residue chemistry summary 12

5.0 Fate and behaviour in the environment 16
- 5.1 Summary of the fate and behaviour of kresoxim-methyl in the environment 16
  - 5.1.1 Transformation 16
  - 5.1.2 Mobility 16
  - 5.1.3 Transformation products 17
- 5.2 Expected environmental concentrations 17
  - 5.2.1 Soil 17
  - 5.2.2 Water 17
  - 5.2.3 Vegetation 18

6.0 Effects on non-target species 19
6.1 Terrestrial species 19
6.2 Aquatic species 19
6.3 Environmental risk assessment 19
6.4 Mitigative measures 20
6.5 Outstanding data requirements and clarifications 20
6.6 References 20

7.0 Integrated efficacy summary 21
7.1 Effectiveness against apple scab caused by *Venturia inaequalis* on apple 21
7.1.1 Kresoxim-methyl on a protectant schedule 21
7.1.2 Curative applications of kresoxim-methyl 22
7.2 Effectiveness against powdery mildew caused by *Podosphaera leucotricha* on apple 23
7.3 Information on the occurrence or possible occurrence of the development of resistance 23

8.0 Toxic Substances Management Policy 24

9.0 Regulatory decision 25

List of abbreviations 27

Appendix I Summary table of toxicology studies 29

Appendix II Nature of kresoxim-methyl residues in animals and plants 35

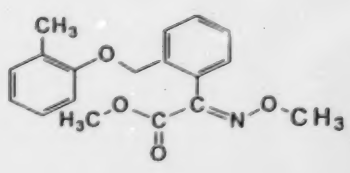
Appendix III Summary tables of environmental studies 39
Table 1 Summary of transformation and mobility data for kresoxim-methyl and the formulated end-use product 39
Table 2 Summary of transformation and mobility data for the major transformation product, BF 490-1 40
Table 3 Expected environmental concentrations (mg a.i./kg dw) of kresoxim-methyl on food sources and in the diet of wild birds and mammals immediately following four applications at the Canadian maximum label rate of 0.225 kg a.i./ha (no transformation) 41
Table 4 Summary of effects of kresoxim-methyl on terrestrial non-target species 42
Table 5 Summary of effects of kresoxim-methyl on aquatic non-target species 44
Table 6 Summary of risk assessment to terrestrial non-target species 45
Table 7 Summary of risk assessment to aquatic non-target species 46
References for Appendix III 46

1.0 The active substance, its properties, uses, proposed classification and labelling

Kresoxim-methyl belongs to the strobilurins class of fungicide. It inhibits mitochondrial respiration by blocking electron transfer at the bc_1 complex in fungi. The protective effect is due to the inhibition of both spore germination and host infection. The curative and eradicative effects are the result of kresoxim-methyl's inhibition of mycelial growth and sporulation.

The commercial formulation, Sovran® Fungicide, is a foliar fungicide for use on apples to control apple scab and powdery mildew. It provides commercially acceptable control of scab and powdery mildew when applied at 90–180 g active ingredient (a.i.)/hectare (ha) and 120–225 g a.i./ha, respectively. A maximum of four applications per season is recommended.

1.1 Identity of the active substance and preparation containing it

Active substance:	Kresoxim-methyl
Function:	Fungicide
Chemical name: (International Union of Pure and Applied Chemistry):	Methyl (E)-2-methoxyimino-2-[2-(*o*-tolyloxymethyl) phenyl]acetate
Chemical name (Chemical Abstracts Service [CAS]):	α-(methoxyimino)-2-[(2-methylphenoxy)methyl]benzeneacetic acid methyl ester
CAS number:	143390-89-0
Nominal purity of active:	94.0%
Identity of relevant impurities of toxicological, environmental and other significance:	The technical material is not known to contain any toxic microcontaminants identified as Track-1 substances in the Toxic Substances Management Policy (TSMP)
Molecular formula:	$C_{18}H_{19}NO_4$
Molecular mass:	313.36
Structural formula:	

1.2 Physical and chemical properties of active substance

Table 1.1 Technical product: Kresoxim-methyl

Property	Result	Comment
Colour and physical state	Pure active ingredient (PAI): white crystals Technical grade active ingredient (TGAI): light-brown powder	
Odour	Odourless	
Melting point and range	PAI: 97.2–101.7°C TGAI: 98–100°C	
Density	PAI: 1.258 g/cm^3 at 20°C	
Vapour pressure	TGAI: 2.3×10^{-6} Pa at 20°C (by extrapolation)	The active ingredient is relatively non-volatile
Henry's Law constant	3.6×10^{-4} Pa·m^3·mol^{-1}	Will not volatilize from moist soil and water surfaces
UV and visible spectrum at 26°C	λ_{max} at 204 nanometres (nm), no absorption at $\lambda > 350$ nm	Minimal phototransformation is expected
Solubility in water at 20°C	PAI: 2.00 ± 0.08 mg/L	Low solubility
Solubility (g/100 mL) in organic solvents at 20°C	Solvent — Solubility *n*-heptane — 0.172 toluene — 11.1 CH_2Cl_2 — 93.9 methanol — 1.46 acetone — 2.17 ethyl acetate — 12.3 acetonitrile — 16.6 *i*-propanol — 0.480	
n-Octanol–water partition coefficient (K_{ow})	log K_{ow} = 3.4 ± 0.02	Potential for bioaccumulation
Dissociation constant (pK_a)	No pK_a value at pH 2–12	Does not dissociate
Oxidizing properties	Stable at 54°C for 14 days Compound contains no moiety that could exert oxidizing properties	
Storage stability	Not applicable to the technical product	

Table 1.2 End-use product: Sovran® Fungicide

Property	Result
Physical state	Granular powder
Formulation type	Wettable granules
Guarantee	50%

1.3 Classification and labelling

1.3.1 Technical kresoxim-methyl

Technical kresoxim-methyl was found to be of low acute toxicity by the oral, dermal and inhalation routes. It was mildly irritating to the eyes, not irritating to the skin and not a dermal sensitizer.

On the basis of the results of the acute toxicity testing, the signal words "Caution Eye Irritant" are required on the primary display panel of the technical active ingredient.

1.3.2 Sovran® Fungicide (48.4% kresoxim-methyl) end-use product

Sovran® Fungicide (48.4% kresoxim-methyl) was considered to be of low acute toxicity by the oral, dermal and inhalation routes. It was mildly irritating to the eyes, not irritating to the skin and not a dermal sensitizer. None of the inert ingredients in the formulation appear on the United States (U.S.) Environmental Protection Agency (EPA) lists of inerts of toxicological concern (all are on list 4B).

On the basis of the results of the acute toxicity testing with the Sovran® formulation, the signal words "Caution Eye Irritant" are required on the primary display panel of this formulation.

2.0 Methods of analysis

2.1 Method for analysis of the active substance as manufactured

A reversed phase – high performance liquid chromatographic (RP–HPLC) method was used for the determination of the active substance and significant impurities (content $\geq$ 0.1%) in the technical product. The method has been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2 Method for formulation analysis

An isothermal capillary gas chromatographic (GC) method was used for the determination of active substance in the formulation. The method has been shown to have satisfactory specificity, linearity, precision and accuracy.

2.2.1 Multiresidue methods for residue analysis

Existing multiresidue methods (MRM) of analysis were found to be suitable for the determination of residues of kresoxim-methyl and its metabolites in fatty (ground beef) and nonfatty (grapes) matrices. Since the MRM analyses for all components of the residues of concern (ROC) in both plant and animal commodities, it may be considered as a singular enforcement method compared with separate methods for plant (350/3-US) and animal (354/1-US and 354/2) matrices (see sections 2.3.2 and 2.3.3). In contrast to method 350/3-US, the MRM also analyses for the parent compound and the metabolite 490M1 separately. Although methods 350/3-US and 354/1-US were also accepted as enforcement methods, method 354/2 was not accepted. Therefore, the submitted MRM is the only method currently accepted for enforcement analyses in meat and meat by-products.

2.2.2 Methods for residue analysis of plants and plant products

The ROC was defined from the apple metabolism studies as the parent compound (kresoxim-methyl) and the metabolites 490M1, 490M2 (free and glucose conjugated) and 490M9 (free and glucose conjugated).

Residues of concern were determined by HPLC with UV detection (270 nm) in apples and apple juice, grapes and its processed commodities (wine, must and marc) and pecans. The analytical method reduces the number of analytes to three by enzymatic cleavage of the glycosides of the metabolites and hydrolysis of kresoxim-methyl to 490M1. Kresoxim-methyl is calculated as 490M1 equivalents. The method limit of quantitation (LOQ) for each analyte in all matrices was reported to be 0.05 parts per million (ppm) and thus 0.15 ppm for all three analytes combined. This method was found to give good recoveries for the analysis of apples (81–105%), apple juice (74–98%), grapes (70–105%), processed grape commodities (76–100%) and pecans (90–130%). The standard deviations measured following spiking at 0.05–5 ppm were indicative of the method having good to satisfactory repeatability. Representative chromatograms of control and spiked samples of apples and grapes showed no interferences from matrix coextractives, or from reagents, solvents and glassware. Good linearity (correlation coefficient, $r = 0.99$ for 490M1, 0.99 for 490M2 and 0.99–1.0 for 490M9) was observed in the range of 0.05–125 μg/mL for the ROC. The interlaboratory validations (ILVs) supported the reliability and reproducibility of the BASF Canada Inc. method for the determination of ROC in apples, grapes and pecans.

2.2.3 Methods for residue analysis of food of animal origin

The ROC for kresoxim-methyl was defined from the lactating goat metabolism studies as kresoxim-methyl and the metabolites BF 490-1, BF 490-2 and BF 490-9 in ruminant tissues and milk.

The petitioner is not proposing a common moiety method. Method 354/1-US (or method 354/1) is proposed to quantify BF 490-9 and BF 490-2 in milk. Method 354/2 is proposed to quantify BF 490-1 and BF 490-9 in liver, BF 490-1 and BF 490-2 in muscle, and BF 490-1, BF 490-2 and BF 490-9 in kidney and fat. Methods 354/1-US and 354/2 determine residues by HPLC with UV detection (270 nm). None of these methods analyses for the parent compound.

The Pest Management Regulatory Agency (PMRA) evaluated the information provided for method 354/1 and found that it is valid. This method was found to give good recoveries for the analysis of whole milk (78–107% for BF 490-2 and 67–118% for BF 490-9). Representative chromatograms of control samples showed interferences for BF 490-2 at the 0.001 ppm fortification level. Because of this interference, the LOQ for both analytes was revised to 0.004 ppm (0.002 ppm for each analyte). The limit of detection (LOD) was determined at 0.002 ppm. Chromatographic peaks for each analyte were well defined and symmetrical. Good linearity (r = 0.997–0.998) was observed in the range of 0.002–1 ppm for both analytes. Method 354/1-US analyses for the most predominant metabolites in milk, BF 490-9 and BF 490-2, and is recommended as the enforcement method for analyses of milk from animals treated orally with kresoxim-methyl.

The PMRA evaluated the information provided for method 354/2 and found that it is valid for analyses in muscle and liver tissues, but not for analyses in kidney and fat tissues. Recoveries were not always within guideline requirements in kidney and fat samples, especially at the stated LOQ of 0.01 ppm for each analyte. Mean recoveries in all tissues were 69–91% for BF 490-1, 81–93% for BF 490-2 and 83–96% for BF 490-9. In two different validation studies, however, recoveries were beyond the acceptable range of 70–130%, and accuracy was beyond the acceptable range of ±20% in fat samples (75 ± 15%, coefficient of variation [CV] = 19% for BF 490-1; 81 ± 20%, CV = 24% for BF 490-2; and 96 ± 26%, CV = 27% for BF 490-9 in one study; in the other study, recoveries were 69 ± 13%, CV = 19% for BF 490-1 [67 ± 20%, CV = 30% at the 0.01 ppm spiking level] and values for BF 490-2 and BF 490-9 were within acceptable ranges). Although the authors argued that detection of BF 490-1 was more important than detection of BF 490-2 and BF 490-9, as evidenced by a cow feeding study, the relatively poor recoveries for BF 490-1 in fat analyses from the two different validation studies does not support the argument for acceptance of this method for fat samples. In one of the two ILVs, kidney analyses indicated that recoveries were slightly beyond the acceptable range at the 0.01 ppm spiking level for all analytes (69 ± 1.3% for BF 490-1, 69 ± 7% for BF 490-2 and 70 ± 9% for BF 490-9), and the overall accuracy for BF 490-2 analyses (CV = 30%) was beyond the accepted range of 20%. Three trials were attempted before the author of the ILV accepted these results, on the basis of acceptance of values slightly beyond acceptable ranges. These results were not accepted by the PMRA because they

were not within acceptable ranges at the stated LOQ of 0.01 ppm and also because of a lack of overall accuracy for the analysis of BF 490-2. It appears that analyses of analytes in kidney and fat at the 0.01 ppm spiking level are problematical, especially when conducted under good laboratory practice conditions.

Generally, control chromatograms were free from interferences for all analytes in four studies. The LOD was determined to be 0.006 ppm in all tissues tested. Chromatographic peaks for each analyte were well defined and symmetrical. Relatively good linearity (r = 0.994–0.999) was observed in the range of 0.002–1 ppm for all analytes.

2.2.4 Analytical methodology for environmental substrates

In soils, one method employing sequential solvent extraction followed by liquid chromatography (LC) and mass spectrometry (MS) (LC/MS/MS) (BASF method no. D9503) has been successfully used to identify and quantitate kresoxim-methyl and the transformation products BF 490-1 and BF 490-5. The LOQ using this method is 0.01 mg/kg soil (0.01 ppm). A second method using sequential solvent extraction followed by GC and electron capture detection (ECD) (BASF method no. D9603) is capable of quantitating kresoxim-methyl and BF 490-1 at 0.5 mg/kg soil (0.5 ppm). BAS 490 F and BF 490-1 would be expected to remain stable in soil stored frozen for a period of up to two years.

BAS 490 F and BF 490-1 were determined in aquatic media containing algae and duckweed mixed with different nutrient media (BASF method no. D9209). The method used solid phase extraction to remove residues of BAS 490 F and BF 490-1 from the water followed by GC/ECD. The LOQ was 25 μg test material/L (25 parts per billion [ppb]).

3.0 Impact on human and animal health

3.1 Integrated toxicological summary (see also toxicology summary tables, Appendix I)

A detailed review of the toxicological database available for the new fungicide kresoxim-methyl has been completed. The data submitted were largely complete and comprehensive. Data evaluation records from the U.S. EPA were available for most of the individual study reviews and were utilized as much as possible in this review. A document prepared by the Joint WHO/FAO Meeting on Pesticide Residues (JMPR) (1998) was also available and was utilized to fill in data gaps where any existed. In general, the studies were well conducted and in conformity with currently acceptable international guidelines and protocols.

Metabolism studies in Wistar rats showed technical kresoxim-methyl to be moderately absorbed, then widely distributed and quickly eliminated with no tissue bioaccumulation. After 96 hours (h), only residual radioactivity was detectable in gastrointestinal content and in or on skin (females only). Major routes of elimination in both sexes were through

urine (9–33%) and feces (66–81% [35–43% through bile]) and none through exhaled air. Following oral administration, high proportions (73% of dose) of unchanged parent compound were found in feces and none in bile. Systemically available kresoxim-methyl was rapidly and completely metabolized to a total of 32 (major and minor) metabolites, which were identified in urine, feces, bile, plasma and kidneys of rats. The alcohol–acid and phenol–acid of the parent compound and their glucuronides were the predominant final biotransformation products.

Studies of acute toxicity following single dosing showed technical kresoxim-methyl to be of low acute toxicity by the oral, dermal and inhalation routes. Primary eye irritation studies in rabbits showed technical kresoxim-methyl to be a mild eye irritant, while primary dermal irritation studies in rabbits showed that technical kresoxim-methyl was not a dermal irritant. Kresoxim-methyl was not a dermal sensitizer when tested in Guinea pigs according to the maximization test of Magnusson and Kligman. The Sovran® formulation (kresoxim-methyl 48.4 %) was of low acute toxicity by the oral, dermal and inhalation routes. Eye irritation studies in rabbits showed that Sovran® was a mild eye irritant, while dermal irritation studies in rabbits indicated that Sovran® was not a dermal irritant. A dermal sensitization study in Guinea pigs showed that Sovran® was not a dermal sensitizer.

Short-term toxicity studies in rodents indicated the liver as the target organ, with increases in serum γ-glutamyl transferase (SGGT) occurring in rats at 8000 ppm (577 mg/kg body weight [bw] per day [d]) and an increase in relative (to body weight) liver weight manifesting in mice at 4000 ppm (909 mg/kg bw/d). A one-year feeding study in beagle dogs, however, failed to reveal liver toxicity at doses as high as 25 000 ppm (714 mg/kg bw/d). The no observed adverse effect levels (NOAELs) in subchronic studies were mice, 1000 and 8000 ppm (230 and 258 mg/kg bw/d) for males and females, respectively; rats, 2000 and 16 000 ppm (146 and 1374 mg/kg bw/d) for males and females, respectively; and dogs, 5000 and 25 000 ppm (138 and 761 mg/kg bw/d) in males and females, respectively.

In the chronic toxicity study in rats, liver toxicity manifested, beginning at 8000 ppm, as increases in liver weight and SGGT levels, the presence of gross and microscopic lesions including cysts, masses, eosinophilic cell foci, mixed cell foci and hypertrophy, and an increase in the incidence of hepatocellular carcinomas in both sexes. In a two-year oncogenicity (feeding) study in rats, once again, at 8000 ppm and above, there were treatment related liver lesions including cysts, masses, eosinophilic cell foci, mixed cell foci, hypertrophy, bile duct hyperplasia and cholangiofibrosis, as well as an increase in the incidence of hepatocellular carcinomas in both sexes. The NOAELs in chronic rat studies were 800 ppm (36 and 47 mg/kg bw/d in males and females, respectively). Supplementary hepatic cell proliferation studies in young adult and fully mature rats showed that treatment with kresoxim-methyl for three weeks induced a 2- to 3-fold increase in hepatocyte proliferation at 16 000 ppm (1140 mg/kg bw/d), with no hepatocyte proliferation (NOAEL) observed at 200 ppm (15 mg/kg bw/d).

In a carcinogenicity study in mice, the NOAEL was 2000 ppm (304 mg/kg bw/d) on the basis of decreased body weight and microscopic liver lesions observed at 8000 ppm (1305 mg/kg bw/d), but there was no evidence of oncogenicity at the highest dose of 8000 ppm (1600 mg/kg bw/d). That the test substance was not carcinogenic in mice suggests that the liver tumour promotion effect observed in the long-term rat studies was rat specific.

Kresoxim-methyl was not mutagenic in either the Ames test using *Escherichia coli* and *Salmonella typhimurium* or in a gene mutation assay with Chinese hamster ovary cells, nor was it clastogenic in a chromosomal aberration assay in primary human lymphocyte cultures or an in vivo mouse micronucleus assay. It also did not cause unscheduled deoxyribonucleic acid (DNA) synthesis in primary rat hepatocytes or unscheduled DNA synthesis ex vivo in rat hepatocytes. These results indicate that kresoxim-methyl is not genotoxic.

Kresoxim-methyl was not teratogenic in rats and rabbits at doses of up to 1000 mg/kg bw/d and did not cause reproductive toxicity in rats fed doses of up to 16 000 ppm (1625 mg/kg bw/d). The NOAEL for developmental toxicity in rats was 1000 ppm (100 mg/kg bw/d) on the basis of reductions in body weight and body weight gain in F_{1b} and F_2 pups and delays of developmental landmarks in F_{1b} and F_2 pups occurring at 4000 ppm. Kresoxim-methyl showed no evidence of neurotoxicity in rats following either acute or subchronic exposure.

Mechanistic studies on induction of liver tumours (S-phase response) in rats, following a single oral gavage dose or three-week feeding, showed that kresoxim-methyl induced an increased cell proliferation (S-phase response) in liver cells after short-term administration. The S-phase induction was reversible within the recovery period.

3.2 Determination of acceptable daily intake

3.2.1 Non-carcinogenic end points

The recommended acceptable daily intake (ADI) for kresoxim-methyl is 0.36 mg/kg bw/d. The most appropriate study for selection of a toxicity end point for chronic dietary exposure was the two-year dietary study in rats with a NOAEL of 36 mg/kg bw/d, on the basis of body weight decreases and biochemical and pathological liver changes observed at 370 mg/kg bw/d and above. The uncertainty factor of 100 is recommended, on the basis of the fact that the test substance was not genotoxic and did not have teratogenic or reproductive toxicity potential, and that the carcinogenic effect in the liver appeared to be mediated through a non-genotoxic mechanism of tumour promotion.

No additional uncertainty or safety factors were deemed necessary; the database was considered adequate. The apparent increased susceptibility identified in the rat reproductive and developmental toxicity study (decreases in body weights of F_{1b} and F_2 pups and delayed developmental landmarks) occurred at a very high dose, 16 000 ppm (1500 mg/kg bw/d), well above the limit dose at which maternal toxicity was clearly evident.

The U.S. EPA also assigned a reference dose (RfD) of 0.36 mg/kg bw/d non-carcinogenic end points, on the basis of a no observed effect level (NOEL) of 36 mg/kg bw/d (set in the two-year rat study), and using an uncertainty factor of 100.

3.2.2 Carcinogenic end points

Chronic toxicity/carcinogenicity, genotoxicity and mechanistic data suggested that the mechanism of liver tumour (hepatocellular carcinomas in rats) induction by kresoxym-methyl was through non-genotoxic "tumour promotion", mediated by stimulation of prolonged cell proliferation, which appeared to be reversible upon cessation of dosing. However, there was insufficient information to ascertain that the stimulation of liver cell proliferation was a threshold effect. Thus, it was considered most appropriate to utilize the quantitative low dose extrapolation (Q_1*) approach to cancer risk assessment. The Q* value calculated by the U.S. EPA for this purpose was readily available, and was utilized for the cancer risk assessment.

The cancer estimate risk number (Q_1*) assigned by the U.S. EPA for kresoxim-methyl was 2.90×10^{-3}, on the basis of female rat liver tumour development rates from the two-year oncogenicity study (Federal Register, vol. 64, no. 111, June 10, 1999).

3.3 Acute reference dose

In the context of low acute toxicity by the oral, dermal and inhalation routes, and absence of relevant evidence of acute toxicity in the appropriate short-term studies, it is not necessary to propose an acute reference dose (ARfD).

3.4 Toxicology end-point selection for occupational and bystander risk assessment

The end-use product, Sovran®, is of low acute toxicity by the oral, dermal and inhalation routes. Sovran® is a mild eye irritant and is not a dermal irritant or a dermal sensitizer.

In repeated dose toxicology studies, the liver was identified as the target organ. There was no evidence of developmental sensitivity, teratogenicity, reproductive toxicity or neurotoxicity.

Exposure to the mixer, loader or applicator would be short term (i.e., four applications per year) and predominantly via the dermal route. As such, the NOAEL of 1000 mg/kg bw/d, on the basis of absence of toxicity at the highest dose tested from the 21-day dermal toxicology study, was considered most appropriate. A full range of parameters were investigated in this study including clinical signs, body weight gain, hematology, clinical chemistry and macroscopic and microscopic pathology. For non-cancer end points, a margin of exposure of 100 to account for intraspecies and interspecies differences is considered acceptable.

Exposure to the re-entry worker would be of an intermediate term (i.e., several weeks) and predominantly via the dermal route. As such, a study longer than the 21-day dermal toxicology study was considered appropriate, as increased toxicity was observed in

female rats and mice following increased duration of exposure. The NOAEL of 146 mg/kg bw/d in the 90-day rat study, on the basis of increases in liver enzymes and liver weights at the next dose, was considered most relevant for the risk assessment for the re-entry workers. As estimates of dermal absorption were not available, dermal absorption was considered to be equivalent to absorption via the gastrointestinal tract (GIT). For non-cancer end points, a margin of exposure of 100 to account for intraspecies and interspecies differences is considered acceptable.

Kresoxim-methyl caused liver cell carcinomas in rats following long-term feeding. The mechanism of tumour induction was determined to be through tumour promotion by induction of prolonged cell proliferation. Cell proliferation was reversible on cessation of dosing. However, there was insufficient information to ascertain that the stimulation of liver cells proliferation was a threshold effect. Thus, it was considered most appropriate to utilize the quantitative low dose extrapolation (Q_1*) approach to cancer risk assessment. The Q* value circulated by the U.S. EPA for this purpose was readily available, and was utilized for the cancer risk assessment.

The Q_1* assigned by the U.S. EPA for kresoxim-methyl was 2.90×10^{-3} $(mg/kg\ bw/d)^{-1}$, on the basis of female rat liver tumour rates from the two-year oncogenicity study (Federal Register, vol. 64, no. 111, June 10, 1999).

3.5 Impact on human health arising from exposure to the active substance or to impurities contained in it

3.5.1 Operator exposure assessment

Sovran® is a 50% wettable granular formulation proposed for agricultural use. Applications would be to apple orchards via airblast equipment and would be performed up to four times per year, with a minimum of 10 days between applications. A farmer could typically treat up to 20 ha per day. A maximum application rate of 225 g a.i./ha has been demonstrated to be efficacious.

Pesticide operator exposure was estimated using the Pesticide Handler Exposure Database (PHED) Version 1.1. The PHED is a compilation of generic mixer, loader and applicator, as well as flagger passive dosimetry data with associated software that facilitates the generation of scenario specific exposure estimates. The PHED estimates meet North American Free Trade Agreement criteria for data quality, specificity and quantity.

To estimate total dermal and inhalation exposure for airblast application, appropriate subsets of A and B grade data were created from the mixer and loader, as well as the applicator PHED database files. The mixer and loader file was subset for open mixing and dry flowable formulations. The applicator file was subset for application by airblast equipment and tractors or trucks with open cabs. The number of replicates for inhalation and dermal data were acceptable. Estimates were derived for individuals wearing one layer of clothing during mixing, loading and application, as well as gloves during mixing and loading. A best-fit statistical measure was used for the exposure estimates.

An average daily exposure (dermal deposition plus inhalation) of 0.065 mg/kg bw/d was derived for mixers, loaders and applicators wearing one layer of clothing, and gloves during mixing and loading. The predominant route of exposure was dermal. As dermal absorption data was not provided, dermal absorption was considered to be equivalent to absorption via the GIT. A lifetime average daily exposure of 0.000 21 mg/kg bw/d was derived.

For the mixer, loader and applicator (i.e., average daily exposure of 0.065 mg/kg bw/d), the margin of exposure for non-cancer end points on the basis of the NOAEL of 1000 mg/kg bw/d in the 21-day dermal study was 15 000. This margin of exposure is considered adequate. For the carcinogenic end point, the lifetime average daily exposure estimate was coupled with the Q_1^* value to yield a risk level of 6.2×10^{-7} for mixers, loaders and applicators. This risk level is considered acceptable.

3.5.2 Workers

Re-entry workers would have contact with foliage during activities such as summer pruning and, following the preharvest interval (PHI) of 30 days, during harvesting.

Exposure estimates for re-entry workers were carried out using dislodgeable foliar residue date (i.e., grapes) and a generic transfer coefficient (i.e., grape re-entry activities). These estimates were considered to provide conservative estimates of exposure to workers contacting treated apple orchard foliage. The dislodgeable foliar residue study was conducted using a kresoxim-methyl formulation on grape vineyards at three locations (Washington, New York and California). Kresoxim-methyl was applied to the grape vineyards using airblast equipment at an application rate of 0.224 kg a.i./ha. Four applications were made, approximately 10 days apart. Sampling occurred immediately before and after each application, and 1, 2, 3, 4, 5, 7, 14, 21, 28 and 35 days after final application. Dislodgeable residues were sampled from grape leaves using a Birkestrand leaf punch sampler. Each sample consisted of 40 leaf punches, and triplicate samples were taken at each time interval, at each site. An untreated control plot was also sampled at each time interval at each site, and an extensive array of field recovery, laboratory recovery, dislodging efficiency, travel recovery and method validation studies were conducted. The analyte was kresoxim-methyl; there was no analysis for transformation products. The application methods, rates and frequency were relevant to the use pattern proposed for Canada.

Dissipation patterns showed pseudo-first-order kinetics with r^2 values greater than 0.9 at all three sites. On the basis of the relative dissipation rates and environmental conditions, the Washington data set was considered most relevant to Canadian conditions, and was used to estimate potential dermal deposition for a worker re-entering a grape vineyard at various postapplication time intervals. The residue values were coupled with a generic transfer coefficient of 15 000 cm^2/h and adjusted for an eight-hour workday and a 70-kg body weight. For workers carrying out re-entry activities on the day of the final application, exposure (dermal deposition) was estimated to be 1.16 mg/kg bw/d. Estimates of exposure declined on subsequent days. Lifetime average daily exposures were also derived for various re-entry scenarios. For workers re-entering treated areas

following expiry of a seven-day re-entry interval, the lifetime average daily exposure is 0.013 mg/kg bw/d.

For the re-entry worker (i.e., a worker re-entering treated orchards on the day of the final application of Sovran®), the margin of exposure for non-cancer end points, on the basis of a NOAEL of 146 mg/kg bw/d in the 90-day rat study, was 126. This margin of exposure is considered adequate. Margins of exposure would increase on subsequent days. For the carcinogenic end point, the lifetime average daily exposure estimates were coupled with the Q_1^* value to yield a risk level of 3.8×10^{-5}, on the basis of a seven-day re-entry interval. This risk level is considered conservative, as some inputs to the exposure assessment were conservative (e.g., the dislodgeable foliar residue study was conducted at the maximum application rate, not a typical application rate). The level of risk is considered acceptable provided (*a*) a seven-day re-entry interval be specified on the Sovran® label and (*b*) registration be conditional upon conduct of a dislodgeable foliar residue study on apple foliage under Canadian use conditions. The PMRA should be consulted during the protocol development phase. For example, the study design should address the transformation product BF 490-1, as the existing study was limited in that it analysed for the parent compound only. Review of the study will provide the basis for a more refined exposure and risk assessment for workers, and a final regulatory decision.

4.0 Integrated food residue chemistry summary (see summary tables in Appendix II)

Metabolism studies submitted demonstrated the fate and disposition of kresoxim-methyl in apples, grapes, wheat, ruminants and rats. The unchanged parent compound accounted for significant residues in wheat, grapes and Mutsu variety apples, but not in Macintosh variety apples. Also, differences in the quantitative nature of residues was demonstrated by comparison of the two apple metabolism studies. The ROC in apples should be defined as parent, 490M1, 490M2 (free and glucose conjugated) and 490M9 (free and glucose conjugated).

The qualitative and quantitative nature of the residue is understood following oral dosing in rats and goats. Kresoxim-methyl was extensively metabolized in both species, with little or no tissue bioaccumulation. On the basis of the animal metabolism studies, the residue of concern was defined as parent compound, 490M1, 490M2 and 490M9. Since the major rat and goat metabolic profiles were similar, a swine metabolism study is not required.

Method 350/3-US, an HPLC method with UV detection (270 nm), was used to determine residues of kresoxim-methyl and predominant metabolites (490M1, 490M2 and 490M9) in plants. This method converts glucosides of 490M2 and 490M9 into their free metabolites and hydrolyses the parent compound to 490M1. Metabolite 490M1 is measured as kresoxim-methyl equivalents. The LOQ for each analyte of the ROC was established at 0.05 ppm, for a total of 0.15 ppm in apples and grapes and their processed commodities, and in pecans. This method was found to give good recoveries and the standard deviations measured with respect to recoveries following spiking at 0.05–5 ppm

were indicative of the method having good to satisfactory repeatability. Interlaboratory validations in apples, grapes and pecans supported the reliability and reproducibility of method 353/3-US.

Methods 354/1-US and 354/2 both use HPLC with UV detection (270 nm) to determine the predominant metabolites (490M1, 490M2 and 490M9) in ruminant tissues. Method 354/1 is considered to be valid by the PMRA for the determination of 490M2 and 490M9 in milk. The LOQ for each analyte was established at 0.002 ppm, for a total of 0.004 ppm in whole milk. This method was found to give good recoveries and is recommended as the enforcement method for analyses of milk from animals treated orally with kresoxim-methyl.

Method 354/2, used for the determination of the predominant metabolites in ruminant tissues, is considered to be valid for analyses in muscle and liver, but not for analyses in kidney and fat. Recoveries were not always within guideline requirements in kidney and fat samples, especially at the stated LOQ of 0.01 ppm for each analyte (total of 0.03 ppm in kidney and fat; total of 0.02 ppm in muscle and liver). The goat metabolism studies indicated that the highest proportions of 490M1, 490M2 and 490M9 were found in muscle, kidney and milk, respectively. Since method 354/2 showed contradictory results for analyses of 490M2 in kidney, as well as for all three analytes in fat, it was concluded that analyses for the most predominant metabolites in these tissues by method 354/2 are not reliable. On the basis of acceptable analyses of the most predominant metabolites in muscle and liver, but unacceptable analyses of the most predominant metabolites in fat and kidney, method 354/2 is not recommended as an enforcement method for meat and meat by-products.

Kresoxim-methyl and its metabolites, 490M1, 490M2 and 490M9, were subjected through the U.S. Food and Drug Administration multiresidue protocols (MRM). Since the MRM analyses for the ROC in both plant and animal commodities, it may be considered as a singular enforcement method compared with separate enforcement methods for plant (350/3-US) and animal (354/1-US and 354/2) matrices. In contrast to method 350/3-US, the MRM analyses for the parent compound and 490M1 separately. Although methods 350/3-US and 354/1-US were also accepted as enforcement methods, method 354/2 was not accepted by the PMRA. Therefore, the submitted MRM is the only method currently accepted by the PMRA for enforcement analyses in meat and meat by-products.

Submitted freezer stability studies in plant matrices indicated that ROC were stable for at least 30 months when stored at less than –5°C in apples and grapes, 12 months when stored at less than –10°C in grapes, apples and apple process fractions, and 6 months when stored at less than –5°C in pecan. The analytical methods (351/2 and 350/3-US = 350/3 ~ D9611) used in the storage stability studies were adequately sensitive and reproducible, with no evidence of interfering residues or background.

Submitted freezer stability studies in ruminant matrices indicated that ROC were stable at –20°C for at least 12 months when stored in whole milk and 6 months when stored in beef tissues. At 13 months, unacceptable stability was observed for 490M1 in liver (67% relative recovery) and for 490M9 in kidney (67% relative recovery).

The results from supervised field trials (method 350/3-US) in representative Canadian zones indicated that the maximum residues in apples, collected 30 days following the last application of Sovran® DF (50% kresoxim-methyl) and treated at 0.88 kg a.i./ha/season (0.98× good agricultural practices [GAP]), were all less than 0.5 ppm. Two residue decline studies followed the same procedures as the supervised field trials, except that samples were collected at 10-, 20-, 30-, 40- and 60-day PHIs. No residues were measured at PHIs of 40 days or more. Considering these results, the proposed maximum residue level (MRL) for the ROC in apples is 0.5 ppm, with a minimum PHI of 30 days.

In a processing study, apples treated with BAS 490 02F (50% kresoxim-methyl) at 1×, 3× or 5× GAP, with a PHI of 30 days, were processed into apple juice and wet apple pomace. A comparison of the residues in the raw agricultural commodity (RAC) with those in each processed fraction resulted in concentration factors of 0.2× for apple juice and 2.6× for apple pomace at a 30-day PHI. The PMRA will recommend an MRL of 0.15 ppm (LOQ) in apple juice to ensure that residues in apple juice do not pose an unacceptable dietary risk. As apple pomace is a livestock feed, an evaluation of the transfer of kresoxim-methyl residues to livestock tissue and milk was assessed in the livestock feeding study.

In the livestock feeding study, dairy cows were fed kresoxim-methyl in a feed premix at levels of 6, 18 and 60 ppm. Results obtained from the analysis of treated animal tissues indicated that 490M1 reached levels of 0.034 ppm in the kidney, and 490M2 and 490M9 did not exceed the LOQ in any tissues when animals were fed a diet containing 6 ppm kresoxim-methyl for 28 days. The anticipated maximum dietary burden in dairy cows resulting from the feeding of wet apple pomace treated with kresoxim-methyl at GAP was not expected to exceed 0.24 ppm. On the basis of the anticipated dietary burden (25× lower than the lowest feeding level of 6 ppm), it is not expected that ROC for kresoxim-methyl will exceed the LOQ for the analytical method for milk, meat and meat by-products. The following study shows, therefore, that expected residues resulting from the feeding of treated apples to ruminants will likely be covered under the following MRLs:

milk:	0.004 ppm (combined residues of BF 490-2 and BF 490-9)*
meat and meat by-products:	0.03 ppm (combined residues of BF 490-1, BF 490-2 and BF 490-9)*

* BF 490-1, BF 490-2 and BF 490-9 are the reference standards for the metabolites 490M1, 490M2 and 490M9, respectively.

These proposed MRLs differ from U.S. tolerances because no tolerance has been proposed for milk in the United States and because definitions for the ROC in food of animal origin differ between the United States and Canada.

Supervised residue trials on pears, grapes and pecans and a processing study in grapes were also submitted.

The results from the supervised crop field trials study in grapes (method 350/3) conducted in the United States showed that the maximum residues in grapes, collected 14 days following the last application of BAS 490 02F (50% kresoxim-methyl) and treated at 0.896 kg a.i./ha/season equivalent to U.S. GAP, were less than 0.793 ppm (highest average field trial [HAFT] = 0.793 ppm). Maximum residues at a 30-day PHI were less than 0.732 ppm. Consequently, an MRL of 1.0 ppm should be established to cover ROC for kresoxim-methyl in or on grapes imported to Canada.

In a processed food and feed study, BAS 490 02F (50% kresoxim-methyl) was applied to grapes at 2.69 kg a.i./ha with PHIs of 1 and 14 days. Data were reported for the 14-day PHI only. The grape samples were processed into grape juice and raisins. A comparison of the residues in the RAC with those in each processed fraction resulted in a concentration factor of 0.1–0.8 for grape juice and 1.5–1.6 for raisins at a 14-day PHI. The maximum combined residues of kresoxim-methyl and its metabolites expected in raisins, on the basis of the HAFT of 0.793 ppm reported from the residue trial study and the maximum concentration factor (1.6×), is 1.27 ppm. The residues expected in grape juice should be covered under the proposed MRL for the RAC (1.0 ppm). An MRL of 1.5 ppm should be established to cover potential residues in or on raisins imported to Canada.

The results from the supervised crop field trials study in pecans (method D9611A ~ method 350/3) conducted in the United States showed that the maximum residues in pecans, collected 44 or 45 days following the last application of BAS 490 02F (50% kresoxim-methyl) and treated at 1.97 kg a.i./ha per season, were all less than 0.15 ppm (LOQ = 0.15 ppm). One residue decline study was also submitted as a portion of these crop residue trials. Sampling occurred at 35-, 55- and 65-day PHIs. Residues were less than 0.15 ppm at all PHIs. Consequently, an MRL of 0.15 ppm should be established to cover ROC for kresoxim-methyl in or on pecans imported to Canada.

The dietary cancer risk from kresoxim-methyl was calculated on the basis of the Q_1^* linear model approach. On the basis of a Q_1^* of 0.0029 mg/kg bw/d, the risk estimate from all dietary sources was estimated to be 2×10^{-6} to 9×10^{-6}, which was considered to be below the level of concern for lifetime cancer risk, because of the following very conservative assumptions used in arriving at this risk estimate: (*a*) 100% of the crops (apples, grapes and pecans) consumed by Canadians from any source (imported or domestically produced) are treated at the maximum label rate; (*b*) in addition, there was a maximum transfer of residues into meat and milk; and *(c)* no allowance has been made for customary culinary practices such as washing, peeling and cooking of either the fruit or the meat and milk. Consequently, the proposed domestic use of kresoxim-methyl on apples and proposed imports of grapes, raisins and pecans treated with kresoxim-methyl does not pose an unacceptable dietary risk to any segment of the population including adults, infants and children, because of the conservative estimate outlined above.

5.0 Fate and behaviour in the environment

5.1 Summary of the fate and behaviour of kresoxim-methyl in the environment

5.1.1 Transformation

The primary route of transformation of kresoxim-methyl is biotransformation by aerobic micro-organisms in both soil and aquatic systems. The major transformation product produced in soil and water is an acid, BF 490-1.

The rate of hydrolysis of kresoxim-methyl is highly dependent on the ambient pH. Under basic conditions (pH 9), hydrolysis is rapid, resulting in the formation of BF 490-1. Under neutral (pH 7) and acidic conditions (pH 5), kresoxim-methyl is more stable and hydrolysis is slower. Phototransformation is not a major route of transformation on soil or in water. In aerobic soil and in aerobic and anaerobic water and sediment, kresoxim-methyl is transformed rapidly. Kresoxim-methyl is not persistent, therefore, in soil, water or sediment under either aerobic or anaerobic conditions. Data regarding transformation processes of kresoxim-methyl are summarized in Table 1 of Appendix III.

5.1.2 Mobility

Laboratory studies of mobility indicated that kresoxim-methyl exhibits low to moderate mobility in most types of soil, but is moderately to highly mobile in sandy soils. Kresoxim-methyl may run off the soil surface and enter surface waters. Field studies indicated that the residues of kresoxim-methyl were primarily detected in the top 0–15 cm layer of soil; therefore, kresoxim-methyl has a low potential to leach under field conditions.

The potential for kresoxim-methyl to contaminate groundwater was evaluated using the Groundwater Ubiquity Score (GUS) assessment method of Gustafson (1989) and the Expert System for Pesticide Regulatory Evaluation and Simulation (EXPRES) model. The calculated GUS of 1.7 falls into the range for non-leachers (<1.8). This indicates that kresoxim-methyl is unlikely to leach to groundwater. For EXPRES, two indices are calculated, leaching potential (LP; a relative measure of the potential of the pesticide to leach to the water table) and leaching index (LI; a relative measure of the potential migration distance of the pesticide), and compared with four pesticides known from field measurements to have leached to groundwater. Kresoxim-methyl was ranked 50th on the LP scale and 59th on the LI scale of the 130 pesticides in the EXPRES database (Table 5.1). Based on the results of the EXPRES and GUS models and terrestrial field dissipation studies, there is a relatively low probability that kresoxim-methyl will cause groundwater contamination when applied in the field. Data regarding the mobility of kresoxim-methyl are summarized in Table 1 of Appendix III.

Table 5.1 Leaching potential of kresoxim-methyl compared with four pesticides known to leach to groundwater

Pesticide	LP rank	LI rank
Picloram	24	18
Atrazine	45	42
Dicamba	47	46
Kresoxim-methyl	50	59
Dinoseb	70	71

5.1.3 Transformation products

One major transformation product, BF 490-1, was produced in aerobic soils and in water and sediment systems. Laboratory studies indicated that BF 490-1 is moderately persistent to persistent in soil and water. Additional laboratory studies found that BF 490-1 was highly mobile and leached through soils. Based on these laboratory characteristics of persistence and leaching, BF 490-1 would be expected to leach to groundwater. However, field trials indicated that BF 490-1 has a low potential to leach under field conditions. Not enough information was available to determine the leaching potential of BF 490-1 using the EXPRES model. In aquatic systems, BF 490-1 is found primarily in the water column, where it may be bioavailable to aquatic organisms. Data regarding the transformation processes and mobility of BF 490-1 are summarized in Table 2 of Appendix III.

5.2 Expected environmental concentrations

5.2.1 Soil

Kresoxim-methyl is proposed for use in Canada on apples at a rate of 0.225 kg a.i./ha, with applications a minimum of 10 days apart, and no more than four applications. The maximum cumulative application rate on soil, taking into account a soil dissipation time 50% (DT_{50}) of 11 days for kresoxim-methyl, is 0.443 kg a.i./ha. Assuming a soil bulk density of 1.5 g/cm^3, application at the maximum cumulative rate (443 g a.i./ha) to bare soil with no interception by foliage and uniform mixing in soil over a depth of 15 cm, the expected environmental concentration (EEC) of kresoxim-methyl in soil is 0.20 mg a.i./kg soil dry weight.

5.2.2 Water

Expected environmental concentrations in water were calculated by assuming a scenario in which the Canadian label rate (225 g a.i./ha) was applied the maximum recommended number of times (four) at the shortest interval allowed between sprays (10 days). To calculate a maximum cumulative application rate, transformation of the parent compound in soil (runoff) and water (direct overspray) was taken into consideration.

Expected environmental concentration in water from direct overspray:
Using the DT_{50} of 1.6 days in water from the biotransformation in the aerobic water and sediment study, the EEC of kresoxim-methyl in water immediately following the fourth application at 0.225 kg a.i./ha is the equivalent of a cumulative application of 0.228 kg a.i./ha. Assuming a scenario in which a body of water 30 cm deep is oversprayed with the equivalent of a cumulative application of 0.228 kg a.i./ha, the EEC in water is 0.08 mg a.i./L water (see Table 7 of Appendix III).

Concentration in drinking water (runoff):
Expected environmental concentrations of kresoxim-methyl in drinking water were estimated from a U.S. EPA Tier I screening model named GENEEC assuming four applications at 225 g a.i./ha and a minimum 10-day interval between applications. Various parameters from laboratory studies were used in the model. Because the model, GENEEC, does not have an air-blast scenario (by which kresoxim-methyl will likely be applied), a ground application scenario with 1% spray drift and an aerial application scenario with 5% spray drift were tested. Four generic EECs were generated. The results are presented in Table 5.2. The peak concentration in drinking water is expected to be approximately 13 μg a.i./L.

Table 5.2 Generic expected environmental concentrations calculated by GENEEC model for deep water bodies (2 m)

Application method	Generic EEC (μg a.i./L)			
	Peak	Averaged over 4 days	Averaged over 21 days	Averaged over 56 days
Ground	13.05	7.62	1.75	0.66
Aerial	12.83	7.54	1.74	0.65

Expected environmental concentration in pond water (shallow water) from runoff:
The peak values generated by the GENEEC model were converted to a 30 cm deep pond to estimate the concentration resulting from a runoff episode. The EEC in shallow pond water resulting from runoff is 0.087 mg a.i./L (87 ppb).

5.2.3 Vegetation

Concentrations of kresoxim-methyl on vegetation were estimated using a nomogram developed by the U.S. EPA from the data of Hoerger and Kenaga (1972) and Kenaga (1973) for use in ecological risk assessment (Urban and Cook, 1986) (see Table 6 of Appendix III). A fresh to dry weight conversion was also calculated. The maximum application rate of 900 g a.i./ha was used, which assumes no transformation occurred, as the half-life ($t_{½}$) of kresoxim-methyl on vegetation is unknown. The EECs were used to estimate the highest concentration of kresoxim-methyl that may be present in a typical diet of wild birds and some common mammals when exposed to maximum application

rates and frequencies (see Table 3 of Appendix III). These concentrations were used to determine the risk to wild birds and mammals.

6.0 Effects on non-target species

6.1 Terrestrial species

Kresoxim-methyl and the formulated end product are non-toxic to earthworms, honeybees and wild mammals. The major transformation product, BF 490-1, was non-toxic to earthworms. Exposure to the formulated end product resulted in toxic effects in beneficial predatory mites and ladybird beetles after a single application below the maximum proposed application rate for Canada. Effects were also observed with a terrestrial vascular plant (lettuce). Kresoxim-methyl is practically non-toxic to wild birds; on a short-term dietary basis, however, dose-related reproductive effects, including damaged (cracked) eggs, infertile eggs, mortality of developing eggs and mortality at hatch (chicks dead in shell), were observed with the bobwhite quail. The NOEL and lowest observed effect level (LOEL) from a reproductive study with the mallard duck were 100 and 500 mg a.i./kg diet, respectively. Data are summarized in Table 4 of Appendix III.

6.2 Aquatic species

Kresoxim-methyl was highly toxic to *Daphnia magna*, rainbow trout and bluegill sunfish on an acute basis and affected the survival of juvenile fathead minnows at 160 μg a.i./L. Although toxic to fish, kresoxim-methyl is not expected to bioconcentrate in fish tissues. Effects were observed in the freshwater algal species exposed to kresoxim-methyl. The most sensitive algal end point was a no observed effect concentration (NOEC) of 12.0 μg a.i./L in *Navicula pelliculosa*, a freshwater diatom. No effects were observed in an aquatic vascular plant. In contrast to the active ingredient, the major transformation product, BF 490-1, was practically non-toxic to *Daphnia magna* and rainbow trout on an acute basis. The toxicity of kresoxim-methyl to marine biota was not reviewed because, under the given pattern of orchard use, the risk of kresoxim-methyl entering the marine environment in Canada is minimal. Data are summarized in Table 5 of Appendix III.

6.3 Environmental risk assessment

Margins of safety, using the estimated environmental concentrations and toxicity end points (NOEC), were used to determine the risk of kresoxim-methyl to terrestrial and aquatic non-target organisms (see Tables 6 and 7 of Appendix III). Kresoxim-methyl will not pose a risk to earthworms, honeybees, wild birds, wild mammals, fish or aquatic vascular plants. Kresoxim-methyl may pose a risk, however, to beneficial predators and parasites, some terrestrial plants, *Daphnia magna* and freshwater algae. Risks to terrestrial plants, *Daphnia magna,* and freshwater algae can be mitigated.

There are some toxicological concerns with the major transformation product, BF 490-1, because of its persistence in water and sediments and occurrence in the environment at high concentrations. Although three acute studies were submitted, the chronic effects of BF 490-1 are still unknown.

6.4 Mitigative measures

To mitigate the effects on non-target terrestrial and aquatic species, buffer zones should be observed. Buffer zones are determined by using the most sensitive end point, from submitted toxicity studies, which represents the non-target group at greatest risk. Buffer zones of 3 and 7 m are required to protect sensitive terrestrial and aquatic habitats, respectively.

6.5 Outstanding data requirements and clarifications

Several data gaps were identified during the course of the review, specifically the bioaccumulation potential and chronic toxicity of the persistent, major transformation product, BF 490-1. Depending on the environmental conditions, BF 490-1 exhibits moderate persistence to persistence in soil and water (see section 8.0, Toxic Substances Management Policy), has low adsorption in soil and sediments and has the potential to leach to and enter aquatic systems. Although BF 490-1 is not acutely toxic, the chronic effects are unknown. As the chemistry of strobilurins is new to the regulatory field, there is limited a priori knowledge of how strobilurin fungicides or their derivatives may partition in the environment under conditions of commercial use and limited knowledge of the chronic effects, especially those of the transformation products. Because the major environmental transformation pathway of the parent compound results in high levels of a persistent transformation product in the environment (BF 490-1), the chronic effects of this product are of concern.

The persistent nature of BF 490-1 in aquatic systems and the multiple applications of the parent compound indicate that there are repeated occasions on which BF 490-1 can enter aquatic systems. As there is a high potential for chronic exposure to occur, a chronic toxicity study (fish life cycle toxicity test, DACO 9.5.3.2) with either the parent (kresoxim-methyl) or BF 490-1 and a suitable freshwater fish species must be submitted.

6.6 References

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7.0 Integrated efficacy summary

7.1 Effectiveness against apple scab caused by *Venturia inaequalis* on apple

Forty-one trials conducted (between 1991–1998) in Canada and the United States (18 and 23, respectively) were submitted in support of the claims on apples. The location and number of these trials were as follows: British Columbia, 4; Nova Scotia, 5; Ontario, 3; Quebec, 6; California, 1; Michigan, 5; New York, 5; Ohio, 6; Pennsylvania, 4; Virginia, 1; and Washington, 1.

7.1.1 Kresoxim-methyl on a protectant schedule

Thirty-one trials included data on kresoxim-methyl on a protectant schedule. Eighteen trials demonstrated that there were significant differences in disease incidence between kresoxim-methyl and the untreated check. Thirteen trials provided data on the basis of more than five applications and lacked statistical analysis; therefore, those trials could be used only as supplemental data.

Application rate:
The data indicated that there were significant differences in disease incidence between kresoxim-methyl (all tested rates) and the untreated check. Fourteen trials provided data on the proposed low rate of 120 g a.i./ha and six trials on the high rate of 180 g a.i./ha. The high rate provided an average of 96% disease control on fruit and 93% on foliage and the low rate provided an average of 89.5% disease control on fruit and 89% on foliage. Eleven trials demonstrated that 90.0 g a.i./ha consistently provided an equivalent percent disease control to the proposed rate of 120 g a.i./ha (96.2% on fruit and 93.8% on foliage) at low to moderate disease pressure. The rate of 90 g a.i./ha also had a higher percent disease control than the commercial standard (96.4% vs. 91.9% on fruit and 94.4% vs. 92.2% on foliage). Under high disease pressure the 120 and 180 g a.i./ha rates provided acceptable disease control in only two of seven and three of five disease ratings on fruits, respectively.

The available data support an application rate of 90 g a.i./ha under low to moderate disease pressure and 180 g a.i./ha under high disease pressure.

Number of applications and timing:
Eight trials included data on kresoxim-methyl applied at the proposed four applications per season as well as at the commercial standard. In those trials kresoxim-methyl at 90 g a.i./ha provided an average 94.6% (on fruit) and 94.8% (on foliage) disease control compared with 87% (on fruit) and 90.8% (on foliage) for the commercial standard. All trials done under high disease pressure used the proposed number of applications and timing.

The available data support the use of four applications per season of kresoxim-methyl at the rate of 90 g a.i./ha under low to moderate disease pressure and 180 g a.i./ha under high disease pressure at one-half inch green or when environmental conditions become favourable for primary scab and continued on a 10- to 14-day interval through second cover.

7.1.2 Curative applications of kresoxim-methyl

Eight trials (between 1994–1998) conducted in Canada and the United States (six and two, respectively) were submitted in support of the curative activity of kresoxim-methyl on apple scab.

Application rate:
Only one rate, 120 g a.i./ha, applied once, was tested in all trials. In seven trials, kresoxim-methyl applied at 120 g a.i./ha under low to moderate disease pressure provided a level of disease control significantly different from the untreated check. One trial under high disease pressure showed that the 120 g a.i./ha did not provide acceptable disease control; this is consistent with the data reviewed previously for protectant applications.

The available data (curative) support an application rate of 120 g a.i./ha under low to moderate disease pressure and 180 g a.i./ha under high disease pressure.

Application timing:
Seven different application times included in eight trials. There were significant differences between kresoxim-methyl and the untreated check in all the trials except one, which had high disease pressure. Six of eight trials demonstrated that kresoxim-methyl applied 48–120 h after infection provided equal or higher percent disease control on fruit than the commercial standard applied 96 h after infection. Four of six trials demonstrated that kresoxim-methyl applied 72–120 h after infection provided equal or higher percent disease control on foliage than the commercial standard at 96 h after infection. One trial showed that under high disease pressure the 120 g a.i./ha did not provide acceptable disease control 85 h after infection; this finding is consistent with the data reviewed previously for protectant applications.

The available data support the claim that kresoxim-methyl provides disease control if applied at 180 g a.i./ha up to 96 h after the infection period.

7.2 Effectiveness against powdery mildew caused by *Podosphaera leucotricha* on apple

Twenty trials conducted over eight years in Canada and the United States (3 and 17, respectively) were submitted in support of the powdery mildew control claims on apples. The location and number of these trials were as follows: British Columbia, 3; California, 4; New York, 6; Pennsylvania, 2; Virginia, 1; Washington, 3; West Virginia, 1. Fourteen trials demonstrated that there were significant differences in disease incidence between kresoxim-methyl and the untreated check. The remaining six trials provided data from more than six applications of kresoxim-methyl and lacked statistical analysis; therefore, those trials could be used only as supplemental data.

Application rate:
The data indicated that there were significant differences in disease incidence between kresoxim-methyl (all tested rates) and the untreated check. Ten trials provided data on the proposed low rate (120 g a.i./ha), four trials on 225 g a.i./ha and five trials on the proposed high rate (240 g a.i./ha).

Two trials compared the low and high rates under moderate and low disease pressure. There was no significant difference between the two rates; however, 240 g a.i./ha provided a higher level of disease control and the same level of control as the commercial standard in both trials. Four trials compared the 120 and 225 g a.i./ha rates. In all cases, the 225 g a.i./ha gave the same or higher level of disease control on leaves. Under high disease pressure, the 225 g a.i./ha rate provided a significantly higher control of fruit russeting.

The available data support an application rate of 120 g a.i./ha under low to moderate disease pressure and 225 g a.i./ha under high disease pressure.

Number of applications and timing:
Kresoxim-methyl applied at 120 and 225 g a.i./ha, using four applications per season, was significantly different from the untreated check in all cases and provided the same level of disease control as the commercial standard.

The available data support the use of four applications per season of kresoxim-methyl at the rate of 120 g a.i./ha at the proposed application times, one-half inch green and continued on a 10- to 14-day interval through second cover.

7.3 Information on the occurrence or possible occurrence of the development of resistance

According to Regulatory Directive DIR99-06 on *Voluntary Pesticide Resistance Management Labelling Based on Target Site/Mode of Action,* the following statements will be incorporated on the Sovran® Fungicide label at next printing.

Group 11 FUNGICIDE (on the primary panel)

For resistance management, please note that Sovran® Fungicide contains a Group 11 fungicide. Any fungal population may contain individuals naturally resistant to Sovran® Fungicide and other Group 11 fungicides. A gradual or total loss of pest control may occur over time if these fungicides are used repeatedly in the same fields. Other resistance mechanisms that are not linked to site of action but specific for individual chemicals, such as enhanced metabolism, may also exist. Appropriate resistance-management strategies should be followed.

To delay fungicide resistance:

- Avoid application of more than two consecutive sprays of Sovran® Fungicide or other fungicides in the same group in a season.
- Fungicide use should be based on an IPM program that includes scouting, historical information related to pesticide use and crop rotation and considers cultural, biological and other chemical control practices.
- Monitor treated fungal populations for sign of resistance development.
- If disease continues to progress after treatment with this product, do not increase the use rate. Discontinue use of this product, and switch to another fungicide with a different target site of action, if available.
- Contact your local extension specialist or certified crop advisors for any additional pesticide resistance-management and/or IPM recommendations for specific crops and pathogens.
- For further information and to report suspected resistance, contact (company representatives) at (toll free number) or at (Internet site).

8.0 Toxic Substances Management Policy

During the review of kresoxim-methyl and Sovran® Fungicide, the PMRA has considered the implications of the federal Toxic Substances Management Policy[1] and the PMRA Regulatory Directive DIR99-03 (*The Pest Management Regulatory Agency's Strategy for Implementing the Toxic Substances Management Policy*) and has concluded the following:

Kresoxim-methyl does not meet the criteria for persistence, as its $t_{½}$ values in water and sediment systems (up to 1.6 days) and soil (up to 11 days) are below the TSMP Track-1 cut-off criteria for water (≥182 days), sediment (≥365 days) and soil (≥182 days). No data were provided for kresoxim-methyl in air.

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1 The federal Toxic Substances Management Policy is available through Environment Canada's web site at www.ec.gc.ca/toxics.

Kresoxim-methyl is not bioaccumulative. Studies have shown that the bioconcentration factors (BCF) are 220, 430 and 52, for whole fish, viscera and fillets, respectively, which are below the TSMP Track-1 cut-off criterion for BCF (≥5000). In addition, the K_{ow} is 3.4, which is below the TSMP Track-1 cut-off criterion of ≥5.0.

The toxicity of kesoxim-methyl is described in Sections 3.0 and 6.0 and Appendices I and III.

Kresoxim-methyl does not contain any by-products or microcontaminants of concern. Impurities of toxicological concerns are not expected to be present in the raw materials nor are they expected to be generated during the manufacturing process. The formulated product does not contain any formulants that are known to contain TSMP Track-1 substances.

In the environment, kresoxim-methyl forms one major transformation product, BF 490-1, which does not meet the criterion for persistence in soil. The $t_{½}$ of BF 490-1 in soil ranged from 35 to 55 days in field studies, which is below the TSMP Track-1 cut-off criterion for soil (≥182 days). However, the $t_{½}$s of BF 490-1 in water (calculated at 335–381 days) and sediment (calculated at 1183 days) are greater than the TSMP Track-1 cut-off criteria for water and sediment. Persistence is a trigger for an examination of the bioaccumulation potential of BF 490-1, for which no data were submitted. Although the K_{ow} is predicted to be less than that of the parent compound, on the basis of the structural changes in kresoxim-methyl during the formation of BF 490-1group), the applicant must submit an K_{ow} study for BF 490-1 for review and confirmation that TSMP Track-1 criteria have not been met.

9.0 Regulatory decision

The active ingredient kresoxim-methyl and the formulated product Sovran® Fungicide, containing kresoxim-methyl for the control of apple scab and powdery mildew in apple orchards in Canada, have been granted temporary registration pursuant to Section 17 of the Pest Control Products Regulations, subject to the generation of the following studies:

- a K_{ow} study for the transformation product BF 490-1
- a chronic toxicity study with either the parent (kresoxim-methyl) or BF 490-1 and a suitable freshwater fish species
- a dislodgeable foliar residue study on apple foliage under Canadian use conditions

List of abbreviations

a.i.	active ingredient
ADI	allowable daily intake
ARfD	acute reference dose
BCF	bioconcentration factors
bw	body weight
CAS	Chemical Abstracts Service
CEPA	*Canadian Environmental Protection Act*
CV	coefficient of variation
d	day
DNA	deoxyribonucleic acid
DT_{50}	dissipation time 50%
EC_{25}	concentration effective against 25% of test organisms
EC_{50}	median effective concentration
ECD	electron capture detection
EEC	expected environmental concentration
EP	end-use product
EPA	Environmental Protection Agency (U.S.)
EXPRES	Expert System for Pesticide Regulatory Evaluation and Simulation
FAO	Food and Agriculture Organization
FOB	functional observational battery
GC	gas chromatography
GIT	gastrointestinal tract
GST-P	glutatione S-transferase, placental form
GUS	Groundwater Ubiquity Score
h	hour
ha	hectare
HAFT	highest average field trial
HPLC	high performance liquid chromatography
ILV	interlaboratory validation
JMPR	Joint WHO/FAO Meeting on Pesticide Residues
K_{oc}	organic carbon adsorption coefficient
K_{ow}	octanol–water partition coefficient
LC	liquid chromatography
LC_{50}	median lethal concentration
LD_{50}	median lethal dose
LI	leaching index
LOAEL	lowest observed adverse effect level
LOD	limit of detection
LOQ	limit of quantitation
LP	leaching potential
MAS	maximum average score
MRL	maximum residue limit
MRM	multiresidue method
MS	mass spectrometry
nm	nanometre

NOAEL	no observed adverse effect level
NOEC	no observed effect concentration
NOEL	no observed effect level
OC	organic carbon content
PAI	pure active ingredient
pH	potential hydrogen
PHED	Pesticide Handlers Exposure Database
PHI	preharvest interval
pK_a	dissociation constant
PMRA	Pest Management Regulatory Agency
ppb	parts per billion
ppm	parts per million
Q_1^*	cancer estimate risk number
PIS	primary irritation score
r	correlation coefficient
r^2	coefficient of determination
R^2	regression coefficient
RAC	raw agricultural commodity
RfD	reference dose
ROC	residue of concern
RP	reversed phase
SGGT	serum γ-glutamyl transferase
TGAI	technical grade of active ingredient
TSMP	Toxic Substances Management Policy
$t_{½}$	half-life
U.S.	United States
WHO	World Health Organization

Appendix I Summary table of toxicology studies

Metabolism
Technical kresoxim-methyl was moderately well absorbed in the GIT. Peak plasma levels were achieved in 1–8 h. It was widely distributed (majority remains in the GIT) with no sex related differences. It was rapidly excreted (±90% administered dose in 48 h), mostly (66–81%) through feces, 9–33% in urine and none in expired air. It has negligible potential for accumulation, <1% administered dose remaining in the carcass by 120 h. It was completely metabolised to 34 metabolites, ultimately conjugated and eliminated as to sulfates and glucuronides. The alcohol–acid, and phenol–acid of the parent compound, and their glucuronides were the predominant final biotransformation products. The parent compound was the most toxicologically significant.

Study	Species and Strain and Doses	LD_{50}; mg/kg bw or LC_{50}; mg/L	Target Organ and Significant Effects and Comments
Acute studies: technical			
Oral	Rats, Wistar, 5/sex 5000 mg/kg bw (limit test)	Median Lethal Dose (LD_{50}) > 5000 mg/kg bw in males and females	No mortality and no treatment related clinical signs or necropsy findings, low acute toxicity.
Dermal	Rats, Wistar, 5/sex 2000 mg/kg bw (limit test)	LD_{50} > 2000 mg/kg bw in males and females	No mortality, erythema at test site, no treatment related clinical signs or necropsy findings, low acute toxicity.
Inhalation	Rats, Wistar, 5/sex 2.04 and 5.6 mg/L	Median Lethal Concentration (LC_{50}) > 5.6 mg/L	No mortality, increased respiration, nasal and ocular discharge occur during exposure, low acute toxicity.
Skin irritation	Rabbits, Vienna White, 2 males, 4 females 500 mg dose	primary irritation score (PIS) (24 and 48 h) = 0.0	Slight erythema in 1/6 animals one hour after dosing, resolved in 24 h, non-irritating to skin.
Eye irritation	Rabbits, Vienna White 0.1 mL (39 mg) dose	maximum average score (MAS) = 4/110	Slight erythema and ocular discharge in all animals within one hour, resolved within 72 h, mild eye irritant.
Skin sensitization (maximization test) of Mugnason and Kligman	Guinea pigs, Dunkin Hartley 0.1 mL intradermal, 5% test material induction and topical 0.3 g, 50% of test material challenge DNCB Positive Control	No erythema or edema 24 or 48 h after challenge	No evidence of sensitization, not a dermal sensitizer.
Acute studies: Sovran® BAS 490 02F (end-use product [EP])			
Oral	Rats, Wistar, 5/sex 5000 mg/kg bw (limit test)	LD_{50} > 5000 mg/kg [bw] in males and females	No mortality, some animals developed diarrhea, which resolved readily, no necropsy findings, low toxicity.
Dermal	Rats, Wistar, 5/sex 2000 mg/kg bw (limit test)	LD_{50} > 2000 mg/kg bw in males and females	No mortality and no treatment related clinical signs nor necropsy findings, low toxicity.
Inhalation	Rats, Wistar, 5/sex 2.04 and 5.6 mg/L	LC_{50} > 5.7 mg/L	No mortality, increased respiration in all animals, low acute toxicity.
Skin irritation	Rabbits, Vienna White 500 mg dose	PIS (24 and 48 h) = 0.0	Slight erythema in 1/6 animals one hour after dosing, resolved in 24 h, non-irritating.

Study	Species and Strain and Doses	LD_{50}; mg/kg bw or LC_{50}; mg/L	Target Organ and Significant Effects and Comments
Eye irritation	Rabbits, Vienna White 0.1 mL (39 mg) dose	MAS = 5/110	Slight erythema and ocular discharge in all animals within one hour, resolved within 72 h, mild eye irritant.
Skin sensitization (Buehler method)	Guinea pigs, Dunkin Hartley 0.5 mL of 60% test material, topical induction, and challenge DNCB Positive Control data used	No erythema or edema 24 or 48 h after challenge	No evidence of sensitization, not a dermal sensitizer.
Short-term toxicity			
STUDY	**Species/Strain and Doses**	**NOAEL (mg/kg bw)/day)**	**Target Organ and Significant Effects and Comments**
90-d dietary	Mice, CrlBR, 10/sex/dose 0, 250, 1000, 4000 and 8000 ppm (0, 57, 230, 909 and 1937 mg/kg bw for males; 0, 80, 326, 1326 and 2583 mg/kg bw for females)	NOAEL = 1000 ppm (230 mg/kg bw/d for males) and 8000 ppm (2583 mg/kg bw/d for females)	Lowest observed adverse effect level (LOAEL) males = 4000 ppm on the basis of decreased bw and increased relative liver weight LOAEL females > 8000 ppm, on the basis of absence of toxic effects at highest dose tested.
21-d repeat-dose dermal	Rats, Wistar, 10/sex/dose 0 and 1000 mg/kg bw/d, 6 h/d	NOAEL = 1000 mg/kg/d in males and females	LOAEL > 1000 mg/kg bw/d, on the basis of absence of toxicity at highest dose tested (limit test).
90-d dietary	Rats, Wistar, 10/sex/dose 0, 500, 2000, 8000 and 16 000 (0, 36, 146, 577 and 1170 for males; 0, 43, 172, 672 and 1374 for females)	NOAEL = 2000 ppm (146 mg/kg/d) in males; 16 000 ppm (1374 mg/kg/d) in females	LOAEL males = 8000 ppm, on the basis of increased SGGT (also seen in other studies) LOAEL females > 16 000 ppm on the basis of absence of toxicity at highest dose.
12-month gavage	Dogs, beagle, 4/sex/dose 0, 1000, 5000, 25 000 (0, 27,138, 714 mg/kg bw/d for males; 0, 30, 146, 761 mg/kg bw/d for females)	NOAEL = 5000 ppm (138 mg/kg/d) in males; 25 000 ppm (761 mg/kg/d) in females	LOAEL males = 25 000 ppm, on the basis of decreased bw, decreased bw gain and decreased food efficiency LOAEL females > 25 000 ppm on the basis of absence of toxicity at highest dose.

STUDY	Species/Strain and Doses	NOAEL (mg/kg bw)/day)	Target Organ and Significant Effects and Comments
Chronic toxicity and oncogenicity			
18-month feeding	Mice, CrlBr, 50/sex/dose 0, 400, 2000 and 8000 ppm (0, 60, 304 and 1305 mg/kg bw/d in males; 0, 81, 400 and 1662 mg/kg bw/d in females)	**Chronic effects** NOAEL = 2000 ppm (304 mg/kg bw/d) in males; 400 ppm (81 mg/kg bw/d) in females **Oncogenicity** No oncogenic effects in either sex	LOAEL males = 8000 ppm (1305 mg/kg bw/d) on the basis of decreased bw and liver and adrenal amyloidosis. LOAEL females = 2000 ppm (400 mg/kg bw/d) on the basis of decreased bw. Not carcinogenic in mice.
Two-year feeding	Rats, Wistar, 20/sex/dose 0, 200, 800, 8000 and 16 000 ppm (0, 9, 36, 370 and 746 mg/kg bw in males; 0, 12, 48, 503 and 985 mg/kg bw in females)	**Chronic effects** NOAEL = 800 ppm (36 mg/kg bw/d) in males; 800 ppm (48 mg/kg bw/d) in females **Oncogenicity** NOAEL = 800 ppm (36 and 48 mg/kg bw in males and females, respectively)	LOAEL males = 8000 ppm on the basis of increased SGGT, increased liver weight and liver histopathology. LOAEL females = 8000 ppm on the basis of decreased bw, decreased bw gain and liver histopathology. LOAEL for liver carcinomas in both sexes was 8000 ppm (370 and 503 mg/kg bw in males and females, respectively).
Two-year feeding	Rats, Wistar, 50/sex/dose 0, 200, 800, 8000 and 16 000 ppm (0, 9, 36, 375 and 770 in males; 0, 12, 47, 497 and 1046 females)	**Chronic effects** NOAEL = 800 ppm (36 and 47 mg/kg for males and females, respectively) **Oncogenicity** NOAEL = 800 ppm (36 and 47 mg/kg for males and females, respectively) LOEL = 8000 ppm (375 and 497 mg/kg for males and females, respectively)	LOAEL in males = 8000 ppm (375 mg/kg bw/d)* on the basis of decreased bw and liver lesions. LOAEL in females = 8000 ppm (497 mg/kg bw) on the basis of decreased bw, decreased bw gain and liver histopathology. Increased incidence of liver carcinomas occurred in both sexes at 8000 ppm (375 and 497 mg/kg for males and females, respectively) and above.
Neurotoxicity			
Acute neurotoxicity	Rats, Wistar, 10/sex/dose 0, 500, 1000 and 2000 mg/kg bw via gavage	NOAEL = 2000 mg/kg bw/d for males and females, no acute neurotoxicity	LOAEL > 2000 mg/kg bw/d No effect on motor activity or functional observational battery (FOB) at highest dose, no other treatment related effect observed.

STUDY	Species/Strain and Doses	NOAEL (mg/kg bw)/day)	Target Organ and Significant Effects and Comments
Subchronic neurotoxicity (90-d)	Rats, Wistar, 10/sex/dose 0, 1000, 4000 and 16 000 ppm (0, 72, 292 and 1180 mg/kg bw/d) in the diet	NOAEL (neurotoxicity) = 1180 mg/kg bw/d for males and females NOAEL (systemic toxicity) = 4000 ppm (292 mg/kg bw/d) No subchronic neurotoxicity	LOAEL (neurotoxicity) > 1180 mg/kg bw/d. No effect on motor activity or FOB at highest dose. LOAEL (systemic toxicity) = 16 000 (1180 mg/kg bw/d) on the basis of significant reductions in bw and bw gain.
Reproductive and developmental toxicity			
Multigeneration	Rats, Wistar, 25/sex/dose F_0; 25/sex/dose, F_1 0, 50, 1000, 4000 and 16 000 ppm (0, 4.75, 95.4, 386 and 1552.3 males; 0, 5.3, 104.7, 426.9 and 1696.8 females)	**Systemic effects** Parental systemic NOAEL = 1000 ppm (104 mg/kg bw/d) **Reproductive and developmental effects** NOAEL = 1000 ppm (104 mg/kg bw/d)	LOAEL for parental systemic toxicity = 4000 ppm, on the basis of decreased bw, of F_0 and F_1 parental animals, decreased kidney weights F_0 and increased SGGT F_0 males. LOAEL for reproductive and developmental toxicity = 4000 ppm, on the basis of decreased pup weights (F_{1b} and F_2) and delayed developmental landmarks (unfolding of ears [F_{1b}], auditory canal [F_2] and eye opening [F_{1b}]). There were no effects on fertility, or reproductive performance at the highest dose 1696 mg/kg bw.
Teratogenicity	Rats, Wistar, 25/dose 0, 100, 400 and 1000 (mg/kg bw/d) via gavage	Maternal NOAEL = 1000 mg/kg bw/d Developmental NOAEL = 1000 mg/kg bw/d No teratogenic effects up to the highest dose tested	LOAEL maternal > 1000 mg/kg bw/d. No maternal toxicity highest dose tested. LOAEL developmental > 1000 mg/kg bw/d. No fetal toxicity at highest dose tested, no teratogenic effects at highest dose tested.
Teratogenicity	Rabbits, Himalayan, 15/dose 0, 100, 400 and 1000 mg/kg bw/d via gavage	Maternal NOAEL = 1000 mg/kg bw/d Developmental NOAEL = 1000 mg/kg bw/d No teratogenic effects up to the highest dose tested	LOAEL maternal > 1000 mg/kg bw/d. No maternal toxicity at highest dose. LOAEL developmental > 1000 mg/kg bw/d. No fetal toxicity at highest dose, no teratogenic effects at the highest dose tested.

Genotoxicity

Study	Species/Strain and Doses	Doses Employed	Significant Effects and Comments
Ames test, point mutation	*Salmonella typhimurium*, TA 98 and TA 100 *Escherichia coli*	0, 20, 100, 500, 2500 and 5000 μg/plate ± S9	Negative
Ames test, point mutation	*Escherichia coli* CM 881 (WP2 trp uvrA pKM 101)	0, 20, 100, 500, 2500 and 5000 μg/plate ± S9	Negative
Mammalian chromosomal aberration (in vitro)	Human peripheral lymphocytes	0, 10, 20 and 40 μg/mL ± S9	Negative

Study	Species/Strain and Doses	Doses Employed	Significant Effects and Comments
Micronucleus assay (in vivo)	Mice CrlBr (5/sex/dose) single interperitoneal dose	0, 500, 1000 and 2000 mg/kg bw with cells harvested at 16, 24, 48 and 72 h post-treatment	Negative for micronuclei, clinical signs of toxicity were observed in all dose groups after 30 minutes.
UDS in vitro (DNA damage and repair)	Rat hepatocytes (Wistar)	0.33, 1.0, 3.33, 10.0, 33.3 and 100.0 μg/mL	Negative
UDS ex vivo (DNA damage and repair)	Rats, Wistar, single dose oral gavage	0, 20, 200 and 1000 mg/kg bw	Negative
UDS ex vivo (DNA damage and repair)	Rats, Wistar, 3/group, three-week feeding	0, 200 and 16000 ppm (0, 4.79 and 441.87 mg/kg bw)	Negative
Mammalian cytogenetics (in vitro)	CHO/HGPRT	0.1, 0.5, 1.0, 5.0, 10.0 and 100.0 μg/mL ± S9 or 1.0, 2.15, 4.64, 10.0, 21.5, 46.4 and 100.0 μg/mL ± S9	Negative

Special studies

Study	Species/Strain and Doses	NOAEL (mg/kg bw)/day)	Target Organ/Significant Effects and Comments
Hepatocyte proliferation S-phase response (single dose)	Rats, Wistar, 3 males/dose 0, 20, 200 and 1000 mg/kg bw by gavage	NOAEL = 20 mg/kg bw, increased hepatocyte proliferation at 200 mg/kg bw and above	LOAEL = 200 mg/kg bw on the basis of two-fold increase in S-phase response at 200 mg/kg bw/d and above after three weeks.
Hepatocyte proliferation S-phase response (three-week dosing)	Rats, Wistar, young adult, 3–5/dose 0, 200 and 16 000 ppm (0, 15 and 1140 mg/kg bw/d) in the diet	NOAEL = 200 ppm (15 mg/kg bw), 2–3 fold increase in hepatocyte proliferation at 1140 mg/kg bw	LOAEL = 16 000 ppm (1140 mg/kg bw/d) on the basis of increased S-phase response (hepatocyte proliferation).
Hepatocyte proliferation (S-phase response) (three-week dosing and two-week recovery (from JMPR report)	Rats, Wistar, 16 months old, 3–5/dose 0, 200 and 16 000 ppm mg/kg bw/d in diet	NOAEL = 200 ppm (15 mg/kg bw), 2–3 fold increase in hepatocyte proliferation at 1140 mg/kg bw	LOAEL = 16 000 ppm (1140 mg/kg bw/d) on the basis of increased S-phase response. S-phase induction was reversible within the recovery period.
Tumour initiation	Rats, Wistar, 10/sex 2388 mg/kg bw via gavage	NOAEL (tumour initiation) > 2388 mg/kg bw Not a tumour initiator	LOAEL > (tumour initiation) 2388 mg/kg bw No increase in glutatione S-transferase, placental form (GST-P) positive foci in liver.
Tumour promotion	Rats, Fischer, at 0, 200, 800, 8000 and 16 000 ppm (0, 10.7, 42.5, 430 and 886 mg/kg bw/d) for six weeks, via diet	NOAEL (tumour promotion) = 800 ppm (42.5 mg/kg bw/d) A possible tumour promoter	LOAEL (tumour promotion) = 8000 ppm (430 mg/kg bw/d) on the basis of a dose related increase in GST-P positive foci at 8000 ppm and above.

Study	Species/Strain and Doses	NOAEL (mg/kg bw)/day)	Target Organ/Significant Effects and Comments
Recommendation for ADI for non-carcinogenic end points The ADI was 0.36 mg/kg bw/d, on the basis of the NOAEL of 36 mg/kg bw/d set in a two-year rat study and using a 100-fold uncertainty factor.			
Q_1^* value:	The Q_1^* assigned by the U.S. EPA for kresoxim-methyl was 2.90×10^{-3}, on the basis of female rat liver tumour rates from the two-year oncogenicity study (Federal Register, vol. 64, no. 111, June 10, 1999).		
ARfD:	An ARfD was deemed unnecessary. No acute end point was selected, as no adverse effects resulting from single exposure were identified in the short-term toxicity studies and acute neurotoxicity study in rats, nor in developmental toxicity studies in the rat and the rabbit.		

Appendix II Nature of kresoxim-methyl residues in animals and plants

Plant metabolism
The unchanged parent compound accounted for significant residues in wheat, grapes and Mutsu variety apples, but not in Macintosh variety apples. Also, differences in the quantitative nature of residues were demonstrated by comparison of the two apple metabolism studies.
The ROC in apples was defined as parent, 490M1, 490M2 (free and glucose conjugated) and 490M9 (free and glucose conjugated).

Matrix	Total rate (kg a.i./ha)	PHI (days)	Identified total radioactive residues [^{14}C] kresoxim-methyl label
Apples (MacIntosh)	3.91	14	0.69 ppm
Apples (Mutsu)	2.40	14	0.32 ppm

Confined crop rotation studies
Not applicable.

Multiresidue methods for residue analysis
Recoveries of kresoxim-methyl residues in grapes ranged from 83 to 106% at spiking levels of 0.05–0.5 ppm using Protocols D and E. Recoveries in ground beef ranged from 107 to 121% at the same spiking levels using Protocol F.

Methods for residue analysis of plants and plant products
Data gathering method 350/3-US: HPLC with UV detection (LOQ = 0.05 ppm per analyte; LOD = 0.025 ppm per analyte).

Matrix	Apples	Apple juice	Grapes	Grape wine, juice (must) and marc	Pecans
Spiking levels (ppm)	0.05–5.0	0.05–5.0	0.05–5.0	0.05–5.0	0.05–0.15
Mean recoveries (%)	81–105	74–98	70–105	76–100	90–130

Interlaboratory validation
Interlaboratory validations indicated good reliability and reproducibility.

Acceptability as an enforcement method
Recommended. Enforcement method equivalent to data gathering method.

Freezer storage stability tests
Metabolism studies indicated that residues of kresoxim-methyl were stable in homogenized apple and grape samples when stored at less than –5°C for 30 and 34 months, respectively. Stability of kresoxim-methyl residues from the freezer storage stability studies are shown below.

Matrix	Storage interval (months)	Temperature (°C)	Spiking levels (ppm)	Corrected recovery in stored samples (%)
apple	1–24	–20	1.0	98
apple	2–12	less than –10	0.34–1.0	80–118
wet apple pomace	2–12	less than –10	1.0	84–102
apple juice	2–12	less than –10	1.0	78–105
grape	2–12	less than –10	1.0	92–114

Freezer storage stability tests
Metabolism studies indicated that residues of kresoxim-methyl were stable in homogenized apple and grape samples when stored at less than –5°C for 30 and 34 months, respectively. Stability of kresoxim-methyl residues from the freezer storage stability studies are shown below.

Matrix	Storage interval (months)	Temperature (°C)	Spiking levels (ppm)	Corrected recovery in stored samples (%)
grape	2–9	less than –10	0.34–0.52	75–118
pecan	2–6	less than –10	1.0	97–100
pecan	6	less than –10	0.25–0.47	82–90

Animal metabolism
In goats, kresoxim-methyl was extensively metabolized, with the predominant metabolites being 490M1, 490M2 and 490M9. Little or no parent compound was observed in tissues.
The ROC was defined as kresoxim-methyl, 490M1, 490M2 and 490M9.

Matrix	Dosing levels (mg/kg bw/d)	Percent of administered dose (ppm)
Tissues	0.25, 0.31, 25.0	<0.10–0.11 (0.19–21.41)
Milk	0.25, 0.31, 25.0	0.03–<0.10 (0.003–0.191)
Feces	0.25, 0.31, 25.0	18–25
Urine	0.25, 0.31, 25.0	59–70

Methods for residue analysis of animal matrices
Data gathering method 354/1-US for milk: HPLC with UV detection (LOQ = 0.002 ppm per analyte; LOD = 0.001 ppm per analyte).

Matrix	Whole milk
Spiking levels (ppm)	0.002–0.1
Mean recoveries (%)	67–118
CV (%)	2.3–23.0

Interlaboratory validation
Interlaboratory validations indicated good reliability and reproducibility.

Acceptability as an enforcement method
Recommended. Enforcement method equivalent to data gathering method.

Data gathering method 354/2 for animal tissues: HPLC with UV detection (LOQ = 0.01 ppm per analyte; LOD = 0.002 ppm per analyte).

Matrix	Skeletal muscle	Liver	Kidney	Fat
Spiking levels (ppm)	0.01–1.0	0.01–1.0	0.01–1.0	0.01–1.0
Mean recoveries (%)	80–96	72–97	69–118	53–109
CV (%)	3.3–14.8	3.4–19.1	8.5–30.3	8.9–26.9

Interlaboratory validation
Interlaboratory validations indicated good reliability and reproducibility for skeletal muscle and liver, but poor reliability and reproducibility for kidney and fat.

Acceptability as an enforcement method
Not recommended (MRM recommended for analyses of animal tissues).

Freezer storage stability tests

Matrix	Storage interval (months)	Temperature (°C)	Spiking levels (ppm)	Corrected recovery in stored samples (%)
Milk	12	less than –20	0.02	108–113
Liver	13	less than –20	0.10–0.12	67–77
Kidney	13	less than –20	0.10–0.12	67–101
Skeletal muscle	13	less than –20	0.10–0.12	90–94
Subcutaneous fat	13	less than –20	0.10–0.12	82–95

Cattle feeding study
Lactating dairy cows fed kresoxim-methyl in a feed premix for 28–29 days at doses of 0, 6, 18 or 60 ppm.

Dose level (mg/kg/d)	Highest measured residue concentration (ppm)					
	Whole milk	Peritoneal fat	Subcutaneous fat	Skeletal muscle	Kidney	Liver
6	<0.002	<0.01	<0.01	<0.01	0.034	nd
18	<0.004	0.041	<0.01	<0.01	0.156	0.08
60	<0.004	0.134	0.03	<0.01	0.387	0.04

Hen feeding study
Because there are no poultry feed items associated with this petition, no data depicting the magnitude of kresoxim-methyl residues in poultry commodities were required.

Number of residue field trials by region

Zones	1	1A	2	5	5A	5B	9	10	11	Total
Required	1	1		4		3			3	12
Submitted	4		2		4		2	2	6	20

Supervised residue trials on apples

Commodity and portion analysed	Formulation	Application			PHI (days)	Highest residues measured (ppm) (several replicates of each sample)
		No.	Total rate (kg a.i./ha)	Percent GAP		
U.S. trials						
Apples	490 02F	8	0.90	100	30	0.22
	490 02F	152	0.88	98	30	0.43
	490 02F	16	0.88	98	10, 20	0.35
	490 02F	16	0.88	98	40, 60	0.15

Processing studies
Apples were treated at 4.48 kg a.i./ha (5× GAP) with a PHI of 30 days. Grapes were treated at 2.69 kg a.i./ha (3× U.S. GAP) with a PHI of 14 days.

Matrix	Concentration factor	Expected residue (ppm)	Proposed MRL
whole apple	—	<0.5	0.5
apple juice	0.2	<0.15	0.15
whole grape	—	<0.8	1.0
grape juice	0.8	0.6	1.0
raisins	1.6	1.3	1.5

Dietary cancer risk assessment
Using DEEM™ Software (Version 6.77) and on the basis of food consumption data from the 1994–1996 Continuing Survey of Food Intake by Individuals (Q_1^* = 0.0029 mg/kg bw), Tier II using supervised trial mean residues for raw agricultural commodities, proposed MRLs for processed commodities and EEC for drinking water.

	Total population	All infants (<1 year)	Children (1–6 years)	Children (7–12 years)	Children (13–19 years)	Adults (20+ years)	Seniors 55+
Lifetime risk	3.0×10^{-6}	8.2×10^{-6}	8.9×10^{-6}	3.4×10^{-6}	2.0×10^{-6}	2.3×10^{-6}	2.3×10^{-6}

No acute dietary risk assessment was conducted, since an acute exposure hazard was not identified in the toxicology review.

Proposed MRLs

Commodity	Proposed Canadian MRL (ppm)	U.S. tolerance (ppm)
Apples	0.5	0.5
Grapes	1.0	1.0
Pecans	0.15	0.15
Apple juice	0.15	None
Raisins	1.5	1.5
Meat and meat by-products of cattle, goats, hogs, horses, sheep	0.03	0.01
Milk	0.004	None

Appendix III Summary tables of environmental studies

Table 1 Summary of transformation and mobility data for kresoxim-methyl and the formulated end-use product

Title	Value	Comments
Soil: kresoxim-methyl		
Phototransformation on soil (25°C)	$t_{½}$ = 70.4 days*	Not a principal route of transformation
Aerobic soil biotransformation	Label A: DT_{50} ~ 15 h Label B: DT_{50} = 4.7 days	Kresoxim-methyl is non-persistent
Mobility (adsorption or desorption)	Loam: organic carbon adsorption coefficient (K_{oc}) = 249 mL/g organic carbon content (OC)	Low to moderate mobility in loam
	Sand: K_{oc} = 320 mL/g OC	Moderate to high mobility in sand
	Loamy sand: K_{oc} = 541 mL/g OC	Low to moderate mobility in loamy sand
	Clay: K_{oc} = 567 mL/g OC	Low mobility in clay
Soil: end-use product		
Canadian field dissipation (0.26 kg a.i./ha × four applications)	Nova Scotia: DT_{50} = 1 day Ontario: DT_{50} < 1 day British Columbia: DT_{50} = 11 days	Sovran® is non-persistent in soil under field conditions
U.S. field dissipation (0.269 kg a.i./ha × four applications)	New York: DT_{50} = 4.5 h Oregon: DT_{50} = 2.9 days California: DT_{50} < 1 h	Sovran® is non-persistent in soil under field conditions
Water: kresoxim-methyl		
Hydrolysis (25°C)	pH 5: $t_{½}$ = 874 days pH 7: $t_{½}$ = 32 days pH 9: $t_{½}$ = 9 h	Principal route of transformation at pH 9
Phototransformation in water	Label A: $t_{½}$ = 14.8 days* Label B: $t_{½}$ = 59.6 days*	Not a principal route of transformation
Aerobic water and sediment biotransformation	Loam system: DT_{50} =1.5 days Sand system: DT_{50} =1.6 days	Kresoxim-methyl is non-persistent
Anaerobic sediment/water biotransformation	Label A: DT_{50} = 0.9 days Label B: DT_{50} = 1.3 days	Kresoxim-methyl is non-persistent

* Under conditions of 12 h light : 12 h dark

Table 2 Summary of transformation and mobility data for the major transformation product, BF 490-1

Title	Value	Comments
Soil		
Aerobic soil biotransformation	Label A: DT_{50} =131 days Label B: DT_{50} = 58.8 days	Moderately persistent
Mobility in U.S. soils (adsorption and desorption)	Loam: K_{oc} = 33 mL/g OC	High to very high mobility in loam
	Sand: K_{oc} not determined	High mobility was reported in sand
	Loamy sand: K_{oc} = 69 mL/g OC	High to very high mobility in loamy sand
	Clay: K_{oc} = 44 mL/g OC	High to very high mobility in clay
Mobility in German standard soils (adsorption and desorption)	Sandy loam with low OC: K_{oc} not determined	Very high mobility in sandy loam soils with low organic carbon (0.90%) content
	Sandy loam with high OC: K_{oc} = 24 mL/g OC	High to very high mobility in sandy loam soils with high organic carbon (2.60%) content
	Loamy sand: K_{oc} not determined	Very high mobility in loamy sand
	Clayey loam: K_{oc} = 17 mL/g OC	High to very high mobility in clayey loam
Mobility (leaching)	not determined	High mobility in aged soils
Canadian field dissipation (0.26 kg a.i./ha × four applications)	Nova Scotia: DT_{50} = 55 days Ontario: DT_{50} = 35 days British Columbia: DT_{50} = 56 days	BF 490-1 is moderately persistent in soil under field conditions
Water		
Aerobic water and sediment biotransformation	Loam system: DT_{50} ~ 462 days Sand system: DT_{50} » 100 days	Moderately persistent to persistent
Anaerobic sediment and water biotransformation	Label A: DT_{50} = 187 days Label B: DT_{50} = 247 days	Persistent

Table 3 **Expected environmental concentrations (mg a.i./kg dw) of kresoxim-methyl on food sources and in the diet of wild birds and mammals immediately following four applications at the Canadian maximum label rate of 0.225 kg a.i./ha (no transformation)**

Organism	Food item	Percent of diet	EEC		
			Food type	Each	Total
Bobwhite quail	small insects	30	178	53.4	108
	forage crops	15	253	38.0	
	grain	55	30.4	16.7	
Mallard duck	large arthropods	30	30.4	9.12	30.4
	grain	70	30.4	21.3	
Mouse	short grass	25	636	159	451
	grain and seeds	50	30.4	15.2	
	leaves and leafy crops	25	1110	277	
Rat	short grass	70	636	445	454
	grain and seeds	20	30.4	6.08	
	large insects	10	30.4	3.04	

Table 4 Summary of effects of kresoxim-methyl on terrestrial non-target species

Organism	Organism and study	NOEC or NOEL	LC_{50} or LD_{50}	Interpretation and comments
Birds	bobwhite quail; acute oral	NOEL = 2150 mg a.i./kg bw	LD_{50} >2150 mg a.i./kg bw	practically non-toxic*
	bobwhite quail; acute dietary	NOEC = 5000 mg a.i./kg diet	LC_{50} >5000 mg a.i./kg diet	practically non-toxic*
	mallard; acute dietary	NOEC = 5000 mg a.i./kg diet	LC_{50} >5000 mg a.i./kg diet	practically non-toxic*
	bobwhite quail; reproduction	LOAEL = 50 mg a.i./kg diet NOEL not determined	not calculated	effects observed
	mallard; reproduction	LOEL = 500 mg a.i./ kg diet NOEL = 100 mg a.i./ kg diet	not calculated	—
Mammals	rat; acute oral	NA	LD_{50}: >5000 mg a.i./kg bw	low acute toxicity
	rat exposed to EP; acute oral	NA	LD_{50}: >5000 mg a.i./kg bw	low acute toxicity
	mouse; 90-d dietary	NOAEL = 1000 mg/kg dw of diet in males; 8000 mg/kg dw of diet in females	NA	increased relative liver weight in males
	rat; 90-d dietary	NOAEL = 2000 mg/kg dw of diet in males; 16 000 mg/kg dw of diet in females	NA	increased levels of SGGT in males
	rat; multigenerational reproduction	Systemic effects NOAEL = 104 mg/kg bw/d in females Reproductive effects NOAEL = 1552.3 mg/kg bw/d in males; 1696.8 mg/kg bw/d in females	NA	decreased kidney, body, and pup weight; increased SGGT in males; delayed developmental landmarks
Invertebrates	earthworms; acute	≥937 mg a.i./ kg	>937 mg a.i./ kg	—
	earthworms; acute exposure to BF 490-1	≥1000 mg BF 490-1/kg	>1000 mg BF 490-1/kg	—
	earthworms; acute exposure to EP	250 mg EP/kg	644 mg EP/kg	—
	honeybees; acute contact	0–25 μg a.i./ bee	>25 μg a.i./ bee	relatively non-toxic**
	honeybees; acute contact with EP	413.5 μg EP/ bee	>413.5 μg EP/ bee	relatively non-toxic**
	honeybees; acute oral with EP (two studies)	(1) not reported (2) 410 μg EP/bee	(1) >98 μg EP/bee (2) >410 μg EP/bee	relatively non-toxic**

Organism	Organism and study	NOEC or NOEL	LC_{50} or LD_{50}	Interpretation and comments
	predators and parasites	not determined	*not determined*	*effects include* mortality, reduction in fertility, decline in number of offspring, variable recovery
Terrestrial plants	soybean, lettuce, radish, tomato, cucumber, cabbage, oat, ryegrass, corn, onion; seed germination, seedling survival, plant height, and dry weight (three studies)	(1) not determined (2) 400 g a.i./ha (3) 390 g a.i./ha	(1) not determined (2) concentration effective against 25% of test organisms (EC_{25}) = 360 g a.i./ha (3) EC_{25} > 390 g a.i./ha	significant reduction in dry weight of lettuce

* According to U.S. EPA classification scheme
** Classification according to Atkins et al. 1981

Table 5 Summary of effects of kresoxim-methyl on aquatic non-target species

Organism	Organism and study	NOEC	LC_{50} or EC_{50}	Interpretation and comments
Freshwater invertebrates	*Daphnia magna*; 48-h, flow-though	160 µg a.i./L	332 µg a.i./L	highly toxic*
	Daphnia magna; acute, static with BF 490-1	not calculated	>100 mg BF 490-1/L	practically non-toxic*
	Daphnia magna; 21-d	55–107 µg a.i./L	not calculated	effect on reproduction at concentrations greater than 107 µg a.i./L
Freshwater fish	Rainbow trout; acute, flow-through	104 µg a.i./L	190 µg a.i./L	highly toxic*
	Rainbow trout; acute, static with BF 490-1	102 mg BF 490-1/L	>102 mg BF 490-1/L	practically non-toxic*
	Bluegill sunfish; acute, flow-through	388 µg a.i./L	499 µg a.i./L	highly toxic*
	Fathead minnow; early life-stage toxicity	87 µg a.i./L (survival of larvae and growth)	>87 µg a.i./L	survival at the highest treatment (160 µg/L) was significantly less than controls
	Rainbow trout; bioaccumulation study, flowthrough	NA	NA	bioconcentration of BAS 490 F unlikely
Freshwater algae	*Navicula pelliculosa* (diatom); Tier II	12 µg a.i./L	29.2 µg a.i./L	—
	Selenastrum capricornutum (green alga); Tier II	12.2 µg a.i./L	59.4 µg a.i./L	—
	Anabaena flos-aquae (blue-green alga); Tier II	295 µg a.i./L	>295 µg a.i./L	—
Vascular plants	*Lemna gibba* (duckweed); Tier II	288 µg a.i./L	>288 µg a.i./L	—

* According to U.S. EPA classification scheme

Table 6 Summary of risk assessment to terrestrial non-target species

Organism	Type of study	NOEC or NOEL	EEC	Margin of safety	Comments
Earthworms	artificial soil	937 mg a.i./kg soil	0.20 mg a.i./kg soil	4690	no risk
Bees	acute contact	28 kg a.i./ha	0.90 kg a.i./ha	31.1	no risk
Predatory mites	laboratory exposure	107.1 g EP/ha	1350 g EP/ha	0.079	potential risk
Ladybird beetles	laboratory exposure	25 g EP/ha	1800 g EP/ha	0.014	potential risk
Bobwhite quail	acute oral	2150 mg a.i./kg bw	108 mg a.i./kg dw	204 days	no risk
	acute dietary	5000 mg a.i./kg dw	108 mg a.i./kg dw	46.3	no risk
	chronic reproduction	50 mg a.i./kg dw (LOAEL)	108 mg a.i./kg dw	not applicable	no risk on the basis of exposure and use patterns and rate of transformation
Mallard duck	acute dietary	5000 mg a.i./kg dw	30.44 mg a.i./kg dw	164	no risk
	chronic reproduction	100 mg a.i./kg dw	30.44 mg a.i./kg dw	3.29	no risk
Rats	acute oral toxicity	5000 mg a.i./kg bw	454 mg a.i./kg dw	>220 days	no risk
	90-d dietary (male)	2000 mg a.i./kg dw		4.4	no risk
	90-d dietary (female)	16 000 mg a.i./kg dw		35.2	no risk
	chronic reproduction	1000 mg a.i./kg dw		2.2	no risk
Mice	90-d dietary (male)	1000 mg a.i./kg dw	451 mg a.i./kg dw	2.2	no risk
	90-d dietary (female)	8000 mg a.i./kg dw		17.7	no risk
Non-target terrestrial plants (lettuce)	Tier II	0.36 kg a.i./ha (EC_{25})	0.90 kg a.i./ha	0.4	potential risk in the absence of mitigation

Note 1: For predaceous mites, the NOEC was estimated as 10% of the LC_{50} calculated from a linear regression model on the basis of mortality of adult mites from Ufer 1994 and Kühner 1993 ($R^2 = 0.72$). The EEC for predaceous mites was on the basis of three applications of the EP at 450 g EP/ha over the adult lifespan of approximately 20 days (Kain and Nyrop 1995, Weeden et al. 1998).

Note 2: For ladybird beetles, the NOEC was estimated as 10% of the EC_{50}, as calculated from the ratio of 60% decline in fertility at an application rate of 300 g EP/ha, assuming a linear dose–response. The EEC for ladybird beetles is the maximum seasonal application rate because over the predicted lifespan of the adult beetle of several weeks to months (Hoffmann and Frodsham 1993), the adult could potentially be exposed to the maximum recommended four applications of the EP (1800 g EP/ha).

Note 3: The assessment of the risk of kresoxim-methyl to wild mammals is on the basis of the evaluation of mammalian toxicity studies by the Health Evaluation Division.

Note 4: For acute toxicity studies with birds and mammals, the margin of safety is reported with the units of days. LD_{50} and NOEC values, as well as food consumption and mean body weights of control animals, were used to determine the amount of time required for a wild animal to accumulate a toxic dose of kresoxim-methyl if exposed to food sources that are contaminated with kresoxim-methyl.

Table 7 Summary of risk assessment to aquatic non-target species

Organism	Type of study	NOEC or NOEL	EEC	Margin of safety	Comments
Non-target freshwater invertebrates (*Daphnia magna*)	chronic flow-through	0.055 mg a.i./L	0.08 mg a.i./L	0.69	potential risk in the absence of mitigation
Fish (fathead minnow)	early life-stage toxicity	0.087 mg a.i./L	0.08 mg a.i./L	1.1	no risk
Algae (freshwater diatom)	Tier II	0.012 mg a.i./L	0.08 mg a.i./L	0.15	potential risk in the absence of mitigation
Aquatic vascular plants (duckweed)	Tier II	0.288 mg a.i./L	0.08 mg a.i./L	3.6	no risk

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